JUNE, 1931.

BRAIN.

PART 2, VOL. 54.

OBSERVATIONS ON THE TREATMENT OF EPENDYMAL GLIOMAS OF THE SPINAL CORD.

BY HUGH CAIRNS, F.R.C.S.,[1]
AND
GEORGE RIDDOCH, M.D.

IT is a commonplace that the spinal cord must be treated with the greatest respect at operation. Interference with it during removal of an extramedullary tumour, by injudicious or rough manipulation, is apt to leave the patient more paralysed than he was before operation, and this risk is greatly increased when attempts are made to remove a tumour from within the spinal cord itself. Removal of tumours from the cervical or upper thoracic spinal cord has at times been followed by respiratory failure or by fatal hyperthermia. It was doubtless for this reason that Elsberg and Beer [1] introduced the "extrusion method" of treatment of intramedullary tumours. By this method at the first operation the tumour is exposed by an incision through the posterior columns, a week later the wound of operation is reopened and as much of the tumour as has meanwhile extruded itself through the incision in the spinal cord is removed. In this way the surgeon aims at removal of tumour tissue with minimum injury to the spinal cord itself. More recently it has been suggested that no attempt should be made to remove intramedullary tumours, but that instead they should be treated by X-rays, surgical measures being restricted to decompressive laminectomy [11].

The object of this paper is to show that there are certain intramedullary gliomas that can be completely removed without serious permanent injury to the spinal cord.

Cerebral gliomas vary greatly in structure, rate of growth and invasive powers, and the same variations are found in gliomas of the

[1] Working under a grant from the Rockefeller Foundation.

spinal cord. Some spinal gliomas grow rapidly, are richly supplied with blood-vessels and have no sharp line of demarcation from the surrounding nervous tissue. Tumours of this type do not lend themselves to surgical removal. But there are others which are quite circumscribed and of slow growth. Two such cases, both of them ependymal gliomas, have come under our care during the past two years, and in each it was possible to remove the tumour, apparently completely, with benefit to the patient. We propose to report these cases in full, because they illustrate many details of the surgical treatment and after-care of patients with intramedullary tumours. The case records show errors in treatment which might be avoided in future. And above all they illustrate the slow but continuous recovery of function of the spinal cord after a tumour has been dissected from its interior. Recognition of the need for long and patient after-treatment is in our opinion of considerable importance in these cases.

Report of Cases.

Case 1. *Intramedullary ependymal glioma of cervical and thoracic spinal cord* (C.4—Th.3). Complete removal by two-stage operation. Great improvement.

History.—Mrs. S., aged 29, referred by Sir Ashley Mackintosh, was first seen on May 5, 1929, complaining of pain in the neck and gradually increasing weakness of all four limbs. She had always suffered from coldness of the extremities and for some years she had had slight pain in the left shoulder when tired. Otherwise she had enjoyed good health until January, 1928, when she began to have pain in the vagina after, and sometimes before, menstruation. This symptom was not severe and had disappeared six months before she came under observation. However, in March, 1928, fourteen months before admission, she began to have disturbances in her limbs, first sensory and then motor. The initial symptom was an intermittent numbness and "wooden feeling" in her right foot, which became worse after she had played tennis. Within a month she began to have numbness and tingling of the ulnar three fingers of the right hand, and later this spread to the index finger. Weakness came on in her lower limbs in June, 1928, at first only as a lack of springiness and an inability to run well. At the same time she found that she could not "do things" with her right hand when it was cold. By August, 1928, there was stiffness of both lower limbs which wore off as the day went on.

These symptoms, though slight, were enough to make her seek medical advice before her impending marriage. She was examined in September, 1928, by an expert neurologist, and as no signs of organic disease were said to have been found she got married. Soon after this her left knee at times began to give way and she occasionally had difficulty in going down stairs; also when

driving her car she found that her feet were apt to slip from the controls. Her disability was not severe, even though there was now also numbness of the left foot, and in January, 1929, she could still walk three miles without becoming tired. In the following month, however, her right lower limb became weak and she was so unsteady that she fell down several times. The tiredness and stiffness of her lower limbs increased, and the symptoms were much worse at the menstrual periods. In March, 1929, six weeks before admission she was no longer able to walk and began to have painful flexor spasms of the lower limbs. At this time also her right hand became so weak that she could not wind up a clock, and tingling sensations began to occur in the tips of the ulnar three fingers of her left hand.

In addition to the disturbances in her limbs, she had suffered for twelve months before admission from pain in the back of the neck, from about the fourth cervical to the second thoracic spines, which was always eased by walking. This pain was not increased by coughing or straining, but sneezing was occasionally followed by a sensation of numbness down her back and lower limbs. During the same period she had had, when walking quickly, an occasional girdle sensation around the waist at the level of the umbilicus. Three weeks before admission a lumbar puncture was done and eight hours later this girdle sensation became so intense that she felt she was being cut in two, and at the same time became collapsed, and suffered from extreme stiffness of her lower limbs and inability to flex her head. These symptoms did not entirely disappear for nine days. During her illness the patient had had occasional headaches and once had vomited. For nine months before admission she had been constipated and had had some difficulty and urgency of micturition, with incontinence on one occasion.

Examination.—The patient had numerous freckles on her face; and on her left upper limb, above the external epicondyle of the humerus there was a hairy mole (1·5 cm. × 0·5 cm.). She was intelligent and co-operative. The optic discs appeared normal. The right pupil was slightly smaller than the left and it reacted poorly to light but well on convergence. There was slight ptosis of the right upper lid and enophthalmos of the right eye. An area of doubtful cutaneous analgesia was found on each side of the face (fig. 1).

There was moderate weakness and wasting, without dystonia, of the small muscles of both hands, especially the right, and to a less extent of the other muscles of the upper limbs, excepting those of the shoulders. All the muscles of the abdominal wall were weak and moderate spastic paresis was present in both lower limbs, more marked on the right side. The tendon jerks of both upper limbs were diminished, more so on the left side. The abdominal reflexes were absent. The knee-jerks were slightly increased and the ankle-jerks normal. The plantar reflexes were extensor and each was accompanied by flexion of the corresponding limb and extension of the opposite limb. Flexor spasms of the lower limbs occurred at times.

The areas of sensory loss are shown in fig. 1. There was complete loss of sensibility to cotton wool and pin-prick below the second thoracic dermatomere.

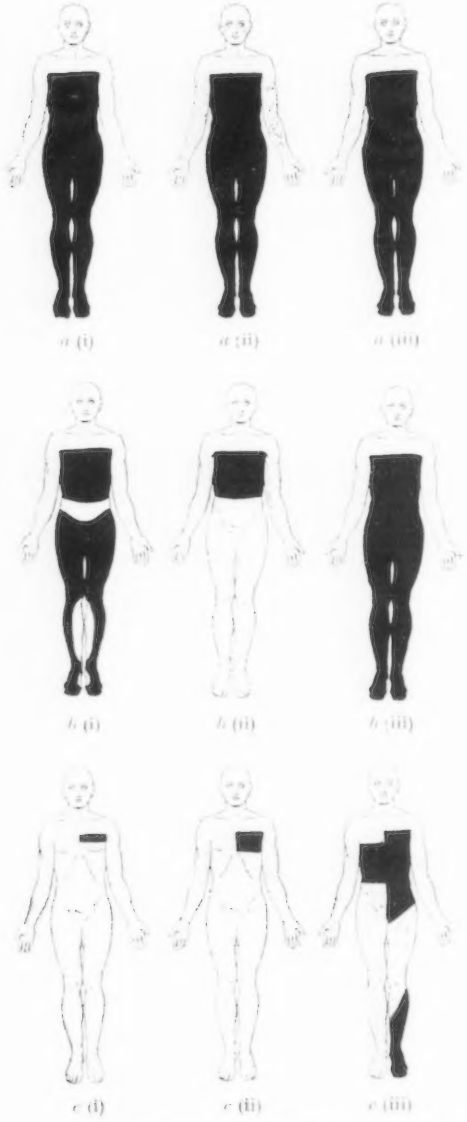


FIG. 1. *a*, *b*, *c*.—*Case* 1. Sensory changes before and after operation. (i) Cutaneous anæsthesia. (ii) Cutaneous analgesia. (iii) Loss of recognition of written numbers (Zahlenschreiben). (*a*, Before operation; *b*, 16 days after operation; *c*, 677 days after operation.)

except for some sparing of the sacral areas.[1] Over the same area vibration sense was lost and there was no recognition of numbers written on the skin (Zahlenschreiben). Postural sensibility was completely lost in the toes, ankles and knees. In the upper limbs sensibility to light touch was preserved, but there was relative cutaneous analgesia and thermo-anæsthesia up to the upper limit of the fifth cervical segmental distribution, slightly higher on the left than on the right side. Postural sensibility and tactile discrimination were normal in the hands and in all the fingers. No areas of cutaneous tenderness could be detected.

There was tenderness of the seventh cervical spine and to a less extent of the adjacent spines. X-rays showed a small cervical rib on each side. The toe-nails were brittle and the patient herself had noticed this during the period of illness. Lumbar puncture revealed a scanty amount of straw-coloured fluid at a resting pressure of 20 mm. of cerebrospinal fluid. No rise of pressure followed jugular compression. There were three cells per c.mm. and the protein content was much increased.

Diagnosis.—There was clear evidence of a lesion extending from at least the fourth cervical to the first thoracic segments. The upper limit was indicated by the boundary of sensory change and the lower by the wasting of the small muscles of the hand, as well as by the sensory dissociation on the upper limbs as compared with the complete sensory loss at the level of the second ribs. The relative absence of pain, the character of the sensory loss, and the sensory and motor indications of the longitudinal extent of the lesion suggested that it was intramedullary. At the same time the occurrence of a girdle sensation of the tenth thoracic level raised the possibility that there might be a double lesion.

First operation.—May 8, 1929. Ether anæsthesia. Five laminæ, from the fourth cervical to first thoracic inclusive, were removed. On opening the dura the presenting spinal cord was seen to be uniformly distended to an extreme degree, and it did not pulsate. The posterior columns were unusually wide and the lower end of the cervical enlargement was slightly yellow in colour. In the middle of the cervical enlargement there was a small area of bluish discoloration which suggested an underlying cyst. However, nothing but a little blood could be obtained by puncture and aspiration of the spinal cord at this point. As there was no pulsation of the cord or flow of cerebrospinal fluid the incision was prolonged upwards by removal of the third cervical lamina, whereupon cerebrospinal fluid began to escape. The diagnosis of an extensive intramedullary tumour was confirmed, and it was felt that it would

[1] Six weeks before the patient came under our care Sir Ashley Mackintosh had found that sensibility to light touch was preserved over most parts of the lower limbs and trunk, though all other forms of sensation were lost up to a level corresponding to the second thoracic segment.

not be right to attempt to remove the tumour without further consultation with the husband, himself a medical practitioner. The incision was accordingly closed in layers, except that the dura had to be left open.

Post-operative course.—For the first twenty-four hours after operation there was tachycardia (pulse rate up to 170), and micturition was frequent. A tiny blister developed on the right middle finger, probably from the application of

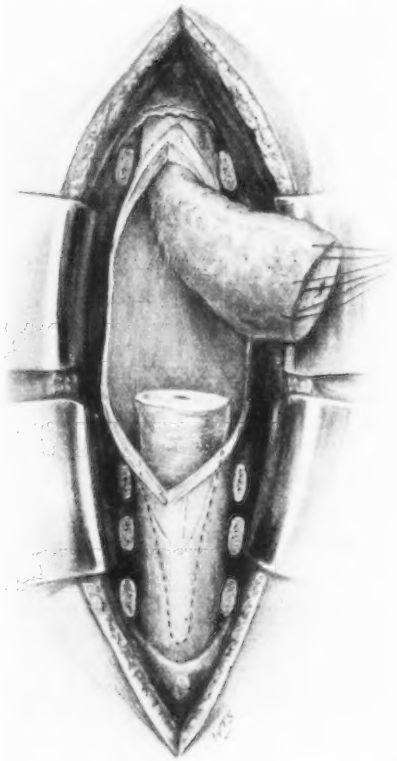


FIG. 2. *Case* 1. Removal of tumour from the interior of the spinal cord. The tumour has been divided and the upper portion is being removed with the aid of traction sutures. The dotted line indicates the extent of the lower portion of the tumour.

a hot-water bottle immediately after operation. The right-sided cervical sympathetic palsy became rather more evident than it had been before operation. No other additional disturbance of spinal function was observed. There was, indeed, slight improvement in sensibility in the sacral and lower lumbar segmental areas, and the patient herself felt that her lower limbs were less

heavy and that she could move them more freely. The flexor spasms of her lower limbs were less painful. This sensory improvement was considered as evidence against a second tumour in the lower part of the cord. At the upper limits of sensory loss light touch was now appreciated on the right side as low as the sixth thoracic segmental area; but on the left side the level was unchanged. Mr. Wilfrid Trotter kindly saw the patient with us at this time and recommended that an attempt should be made to remove the tumour.

Second operation.—May 20, 1929. Ether anæsthesia. The swollen spinal cord was once more exposed through the old wound. A posterior vertical incision was made in it slightly to the left of the middle line, partly because the surface vessels were rather more numerous on the right side and partly with the object of avoiding as far as possible injury of the nerve supply of the right hand. At a depth of 0·2 cm. the surface of a soft, grey tumour was encountered.

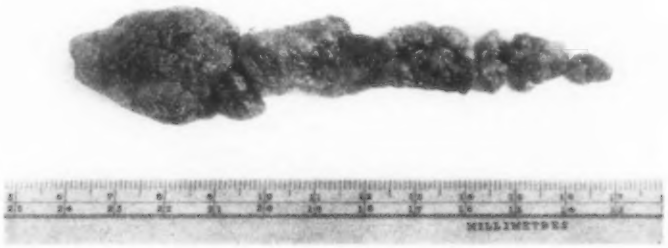


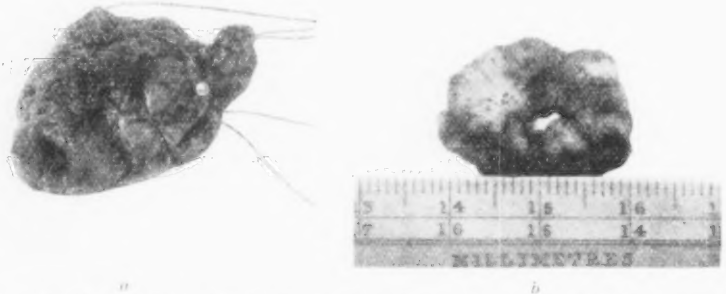
FIG. 3.—*Case* 1. Tumour after removal.

It was circumscribed and could be gently separated from the surrounding spinal cord by dissection with moist pledgets of cotton wool. This was rather tedious and the actual removal of the tumour took two hours. As shown in fig. 2, the tumour was first separated completely from the cord at its widest circumference, and was divided transversely. The upper portion was next removed, traction sutures being used to control its position during the dissection. The tumour narrowed at its upper end, where it was lying at a depth of 0·4 cm. from the posterior surface of the cord. When this part had been dislodged cerebrospinal fluid began to well up into the bed of the tumour. Removal of the lower portion was more difficult because here the tumour was narrower and softer. It was first of all necessary to extend the incision downwards. The spinous processes and laminæ of the second to fourth thoracic vertebræ were removed. The lower part of the tumour came away in fragments but the removal appeared to be complete (fig. 3).

After the tumour had been removed the part of the spinal cord which it had occupied appeared as a flat ribbon up to 2·5 cm. wide and covered by a thin film of blood-clot. The incision in the spinal cord was about 1·1 cm. long

and was estimated to have extended from the fourth cervical to the third thoracic segment. It was impossible to close the dura, which was for the most part overlapped by the flattened spinal cord. The muscles and skin were closed with interrupted fine silk sutures. Apart from a slight fall of blood-pressure and rise of pulse-rate, there had been no appreciable change in the patient's condition throughout the course of the operation.

Pathological examination.—S.D. 1103, 1929. The tumour (fig. 4) after fixation measured 11 cm. long and up to 2·5 cm. in circumference, and weighed 14 grm. At the upper end was a conical depression 0·5 cm. deep (fig. 4*a*). The lower end was tapered like a bullet. The outer surface of the tumour was smooth. Its cut surface consisted of faintly lobulated soft tissue which was in places pink in colour and in others hæmorrhagic. Transverse sections of the tumour in its widest part showed a cleft 0·7 cm. by 0·15 cm. (fig. 4*b*) which

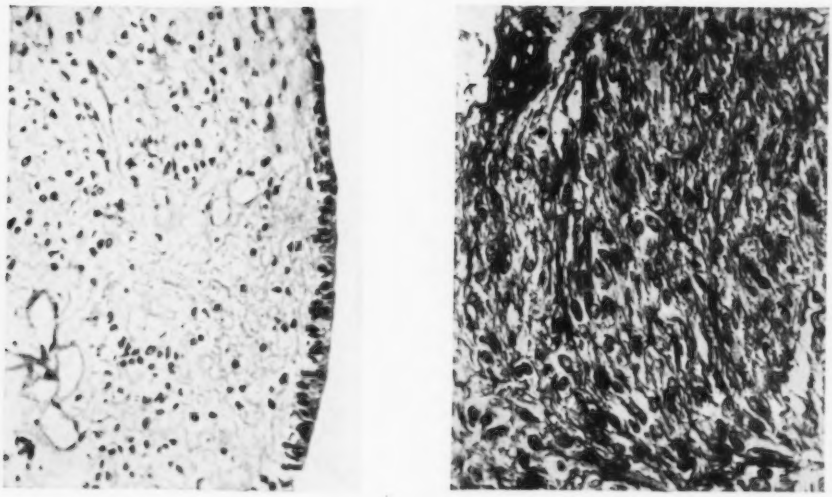


a *b*

FIG. 4.—*Case* 1. (*a*) Upper portion of tumour to show conical depression in the extreme upper end. (*b*) Transverse section of tumour, showing central cavity.

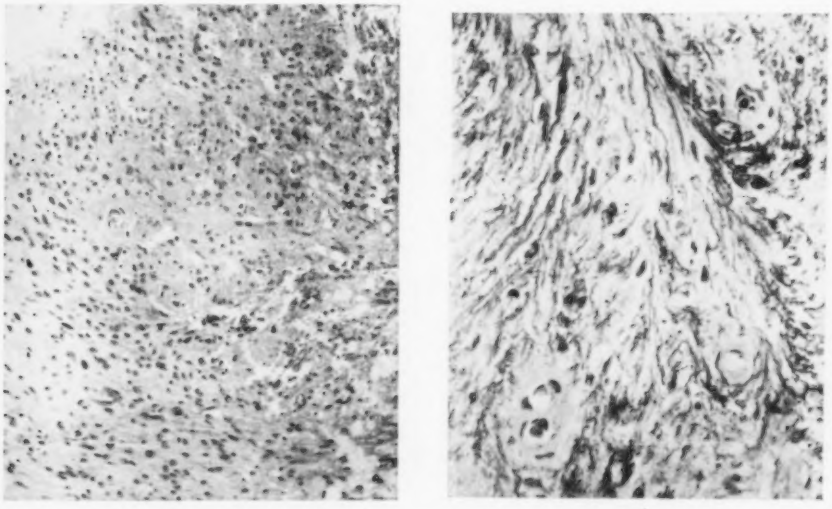
extended into the upper portion of the tumour, where it divided into two smaller clefts. No cleft could be found in the lower, narrower part of the tumour. Histological examination showed an ependymal glioma (Plate III, fig. 5). The central cavity was lined by ependymal epithelium. Further remarks on the pathology of the tumour are given in the body of the paper.

Post-operative course.—The disturbance of spinal function after removal of the tumour was less than we had expected. There was no respiratory embarrassment. When the patient began to regain consciousness her pulse-rate rose rapidly from 120 to 170 and it remained at this level for four hours, falling gradually to normal during the next three days. The temperature did not rise higher than 99·6° F. For a few hours after operation the right thigh was warm, the left thigh cold. At this time also her left lower limb was completely paralysed and the movements of her left upper limb were very ataxic: the limbs on the right side were only slightly worse than before operation. Spontaneous lateral nystagmus was also observed during this period, and for the next five days both pupils were very small, the right being smaller than the left, and



a *b*

FIG. 5, *a*, *b*.—*Case* 1. Histological sections of tumour. (*a*) showing epithelium lining central cavity. Iron hæmatoxylin and van Gieson's mixture, × 175. (*b*) Showing ependymal spongioblasts. Heidenhain's iron hæmatoxylin, × 300.



a *b*

FIG. 10, *a*, *b*.—*Case* 2. Ependymal glioma. (*a*) Hæmatoxylin-eosin. (*b*) Phosphotungstic acid hæmatoxylin, × 450.

To illustrate paper by Hugh Cairns and George Riddoch.

there was considerable enophthalmos on both sides. For several days the knee-jerks were diminished, the ankle-jerks absent. The lower limbs were more flaccid than before operation. To our surprise the patient passed urine voluntarily and freely immediately after the operation: there was, however, increased frequency, and, as before operation, some urgency.

Convalescence was uneventful until the dressing was done on the tenth day when it was found that the centre of the wound was bulging. With the mistaken idea that there might be a hæmatoma a probe was inserted into this bulging area, and a leakage of cerebrospinal fluid was thus unfortunately established. Three weeks after operation the patient had what was evidently a slight attack of meningitis and also developed retention of urine and cystitis.[1] The leak continued intermittently for two weeks, but was then controlled by aspiration of the bulging area and by lumbar puncture, which incidentally showed that there was now a perfectly free flow of cerebrospinal fluid in the spinal subarachnoid space, and that therefore there was little likelihood of a second tumour in the lower part of the spinal cord. Eventually, on July 13, 1929, a further operation was done to repair the weakness of the scar, which was undoubtedly due to reliance on fine silk sutures for approximation of the muscles.

Recovery of voluntary power.—As noted above, the left lower limb was completely paralysed for a few hours after removal of the tumour, but thereafter voluntary power began to return. Movements of the right lower limb were but little affected. By the sixth day the patient could flex and extend her left lower limb at the hip and knee, but movements at the left ankle-joint were still very weak; her right lower limb was by this time quite as strong as it had been before operation. Recovery was evidently delayed by the attack of meningitis, for during the fourth and fifth weeks of convalescence no improvement occurred in the movements of her lower limbs. The patient walked for the first time ten weeks after removal of the tumour. She was discharged from the nursing home one week later. Walking was at first very imperfect owing to ataxia from loss of postural sensibility, weakness of her left lower limb and severe pain in her right knee. There was hyperextension of the knees on standing and occasional inversion of the ankles on walking. These disabilities gradually disappeared without the use of orthopædic appliances. By April, 1930, eleven months after removal of the tumour, she was able to walk a mile or more without any assistance, and soon was able to stand alone for long periods and to drive a motor car. When examined in July, 1930, her gait was still slightly ataxic and she was a little unsteady in performing Romberg's test, but these disabilities had entirely disappeared when she was last seen in March, 1931, twenty-two months after operation, and her walking was not restricted in any way. Movements of extension recovered before those of flexion, and her right

[1] Cerebrospinal fluid, withdrawn by lumbar puncture on June 20, 1929, contained 130 white cells per c.mm.; finely granular oxyphils, 2 per cent.; lymphocytes, 90 per cent.; coarsely granular oxyphils, 8 per cent. Protein, ·055 per cent. Cultures were sterile.

lower limb recovered before the left, though when the patient was last seen voluntary power was equal in the lower limbs.

Voluntary power of her upper limbs improved very quickly after removal of the tumour, recovery of the left side, the side that had been stronger before operation, lagging behind that of the right, doubtless because the incision in the spinal cord had been made to the left of the middle line. Within two weeks she was conscious of improvement in the strength of her hands, and six weeks after operation her handwriting became as good as it had been before the onset of her illness and she was able once more to do fine needlework. When she was seen twenty-two months after operation she said she could use her upper limbs freely and normally, but there was still some weakness and wasting of the small muscles of the hands and of the extensor carpi ulnaris on each side. Recovery of trunk movements followed the same sequence as that of the limbs. Five weeks after operation chest expansion was much better on the right side than on the left, and the right rectus abdominis contracted much more strongly than the left. Fourteen months after operation movements of the trunk were almost normal and equally strong on both sides.

Recovery of reflex function.—Immediately after operation the ankle-jerks were absent and the left knee-jerk was diminished. The right ankle-jerk was first elicited on the sixth day after operation and the left ankle-jerk returned one week later. Eventually the tendon-jerks of the lower limbs became slightly brisker than normal. In the upper limbs the tendon-jerks were all present after operation, but for some months they were diminished on the right side, and then became equal on both sides. The abdominal reflexes were first observed, on the right side only, six months after operation. At the last examination, twenty-two months after operation, the left lower abdominal reflex was diminished, but the others were brisk. At this time the left plantar reflex was still extensor, but only a flexor response could be obtained on the right side. Flexor spasms of the legs ceased after removal of the tumour, though for the first few days the patient had the sensation of slight spasms at the left knee.

Micturition was not affected by removal of the tumour, but when meningitis occurred the patient had increase in frequency, and then retention of urine, which persisted for eleven days. For a few weeks afterwards control of micturition was imperfect, and for some time there was urgency of micturition on excitement. The patient was averse to taking much fluid by mouth and her urine remained scanty (10 oz. per day), offensive, and contained pus and albumen, in spite of the fact that there was no residual urine. This trouble cleared up after the administration of large quantities of fluid by rectum. Nocturnal frequency persisted for some months, but eventually micturition became quite normal, apart from occasional attacks of urgency. The bowels had been constipated before operation and they remained so afterwards, though rather less aperient was necessary than before.

Recovery of sensation.—No accurate tests were made for some days after removal of the tumour, but there was evidently increased loss of postural

sensibility of the left side, as indicated by the extremely ataxic movements of her left upper limb for some hours after operation. Numbness and tingling persisted in her right hand for twenty-four hours, but thereafter her hands felt normal, and her lower limbs also began to feel less heavy and stiff. There was for some months numbness of her legs on waking in the mornings.

Six days after operation, pin-pricks were appreciated in patchy fashion on her lower limbs up to the level of the first lumbar segmental area, and cutaneous analgesia on the arms began to diminish so that its upper level was difficult to define. The charts (fig. 1 *b, c.*) show the main features of sensory recovery. On the sixteenth day after operation complete anæsthesia to cotton wool was found in two distinct areas, an upper area from Th. 2 to Th. 9 and a lower area which extended from Th. 11 to the lower lumbar segments. This lower area was found to have disappeared completely when the patient was next examined on the forty-sixth day. Subsequently the area of anæsthesia to cotton wool was smaller than the area of analgesia to pin-prick.

The charts show that during the process of recovery there was considerable dissociation of sensibility to cotton wool and pin-prick and the recognition of written numbers, and they indicate that the return of sensibility to light touch and to pin-prick was fairly rapid and complete, except at and immediately below the segmental level corresponding to the lower portion of the tumour; whereas Zahlenschreiben and other forms of sensation conveyed by the posterior columns recovered very late. It is not surprising that the posterior columns were the last to recover, in view of their thinness as seen at operation and the manipulation that was necessary for removal of the tumour. For a long time, indeed, we were in doubt as to whether any appreciable recovery of postural sensibility would occur. Slight return of the appreciation of passive movement, but not of its direction, was evident at the right ankle six days after operation, and on the sixteenth day there was evidence of further improvement on the right side, but still complete absence of postural sensibility in the left lower limb. Six weeks after operation, however, it was found that there was no longer any appreciation of posture in the lower limbs. This retrogression was probably due to the attack of meningitis and cystitis which had set in in the fourth week after operation. It has been shown [14] that toxæmia from cystitis will depress the reflex functions of the spinal cord, and it is possible that conduction of the long tracts is also depressed at the same time. When the patient first began to walk she was very ataxic. No marked return of postural sensibility was observed until six months after the operation, when the patient began to appreciate the direction of movements at her knee- and ankle-joints, rather better on the right side than on the left. When examined, fourteen months after operation, she had accurate appreciation of passive movements and of their direction at the right ankle, and to a less degree at the left ankle, and postural sensibility was beginning to return in the toes. Twenty-two months after operation passive movements and their direction were appreciated normally at the right big toe and almost normally at the left big toe. For fourteen months after operation she had been quite

unable to recognize numbers written on the skin anywhere below the third thoracic segmental level, but she then began to name correctly some numbers written on her right lower limbs. Twenty-two months after operation written numbers were recognized on the right side of the trunk down to the sixth thoracic segmental level, and were at times appreciated in both lower limbs (fig. 1 *c*). Vibration, however, was still not appreciated below the second thoracic segmental level. From the time of the first post-operative tests, postural sensibility, tactile localization, vibration and the recognition of numbers were perfect in the upper limbs.

The recovery of function of the spino-thalamic tracts was characterized by a dissociation in which the loss to cold was more extensive than to heat, and the loss to heat more extensive than that to pin-prick. The differences in extent of these areas of sensory loss were for the most part slight.

Sensations of tightness and prickliness occurred once in her lower limbs, about a year after operation, after the patient had walked a long distance, but they did not return.

After operation the patient no longer suffered from cold feet as she had done before. Her toe-nails became much softer, but did not grow any faster. The right pupil remained slightly smaller than the left and its reactions to light and shade were rather sluggish.

Comment.—The result in this case may be considered satisfactory, though doubtless it would have been more rapidly attained, and without any infection of the bladder, but for the occurrence of slight meningitis during convalescence. The amount of recovery of spinal function, as the result of enucleation of the tumour, has been very considerable. The most surprising restoration has been in postural sensibility, in view of the unusual extent and severity of the loss in the lower limbs before operation, the extreme thinness of the posterior columns as observed at operation, and the interference with them that was necessary for removal of the tumour.

The encouraging result in this case prompted us to deal radically with yet another case that appeared a year later. As will be seen from the record that follows, the diagnostic problems were more difficult than in Case 1, and our inability to recognize that the tumour was intramedullary and not extramedullary before and during the early stages of the operation undoubtedly made the result less successful than it would otherwise have been.

Case 2. Intramedullary ependymal glioma of thoracic spinal cord (Th. 3—Th. 5). Initial symptom of severe "intercostal neuralgia." Complete removal of tumour at one-stage operation. Improvement.

History.—Mrs. C., aged 32, was referred by Dr. Warren Crowe on March 11, 1930, complaining of pain in the right side of the thorax and increasing weak-

ness of her lower limbs. She had had no serious illnesses until February, 1929, when, after an attack of "influenza," she began to suffer from pain in the lower part of the right scapular region. The pain was at first dull in character and occurred in attacks lasting about one day and followed by two days of complete freedom. It was brought on or aggravated by bending, coughing and sneezing. As time went on the intervals between the attacks shortened. In June, 1929, it became much sharper and spread "straight through" the right side of the chest to the front at the same level. The pain was almost continuous, but violent attacks would come on suddenly and would last for five minutes at a time, during which she would stand quite still and hold her breast, and send her maid for aspirin. This pain was at times worse than labour pain. It was brought on or so aggravated by sitting that for six weeks she preferred to take her meals standing at the mantelpiece. Any attempt to stoop down made the pain worse, she was afraid to blow her nose, and she "lived in terror" lest she should get a cold. At nights she lay with a pillow under each scapula to relieve the soreness of her back. In August, 1929, six months after its onset, the pain became less severe, and she was able once more to sit down for meals. It now spread around the right side of the chest wall as a band about four inches wide. As the pain decreased in intensity, the patient became conscious of a tingling, itching sensation in the same area. The pain passed off in September, 1929, leaving only slight soreness.

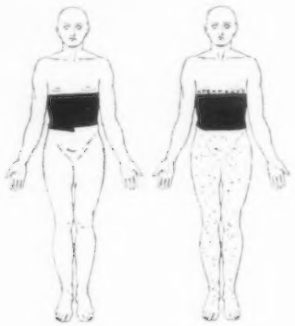
During the period of pain the patient had been treated for "neuritis" by drugs, vaccines, extraction of teeth, electrical treatment and massage. In August, 1929, as the pain was diminishing, she thought she was getting better, but already she was having some difficulty in walking up and downhill. From that time onwards her lower limbs gradually became weaker. On one occasion her right knee gave way and she fell. By December, 1929, she could not walk without support and had to give up all her usual domestic activities. Her knees crackled very much as she walked. At this time she began to have a constant sensation as of a band of iron encircling the trunk at the costal margin, at a slightly lower level than the original pain, and more noticeable during walking. She now became conscious also of impairment of the sensation in her lower limbs. The lower limbs became increasingly heavy and troublesome, and flexor spasms occurred in the mornings. At the time of her admission to the nursing home in March, 1930, she could not walk or stand, though she could still move her lower limbs.

For six months before admission she had suffered from slight difficulty and delay of micturition. For four months her bowels, hitherto regular, had been very constipated, and on one occasion, one month before admission, she was incontinent of fæces. She had been troubled also with flatulent dyspepsia. Throughout the illness she had been conscious of a constant uncomfortable sensation of bodily heat, and she had also felt a loss of initiative and diminished emotional response.

Until the birth of her first child nine years before she had been slim, but subsequently had increased in weight.

Examination.—The patient was very stout and weighed nearly 15 st. (210 lb.). She was slow mentally but on the whole was a good witness. Her speech and articulation, discs, pupils and cranial nerves were normal. Her upper limbs also were unaffected. There was, however, marked weakness of her abdominal muscles and spastic paresis of her lower limbs, right more than left. The only abdominal reflex obtained was the left epigastric. Her knee- and ankle-jerks were much increased and the plantar responses were extensor.

At the fifth thoracic segmental level on the right side there was a zone of cutaneous tenderness below which cutaneous sensibility was lost. Sensibility to light touch was abolished over the front of the abdomen, but not on the back (fig. 6 *a*). There was complete analgesia to pin-prick from the sixth to the tenth thoracic dermatomeres and below this relative analgesia, except in



a *b*

FIG. 6.

the sacral areas where sensibility was almost normal (fig. 6 *b*). Sensibility to heat and cold were slightly diminished below the sixth thoracic level. Postural sensibility was completely lost in the toes and in the right ankle. Vibration, and numbers on the skin (Zahlenschreiben) were not appreciated below the fifth thoracic segmental level. The sensory disturbance was greater on the front than on the back of the trunk. There were no sensory changes in the upper limbs, but after lumbar puncture a dragged pin felt distinctly sharper above the second thoracic level than below it.

Palpation of the spinous processes of the second and third thoracic vertebræ produced deep-seated discomfort which persisted after pressure had ceased. The toe-nails were brittle and the patient stated that they had not grown at all for six months. Examination also showed a small post-anal dimple. X-ray examination of the spine was negative.

Lumbar puncture yielded a very slightly yellow fluid under a pressure of 195 mm. There was no rise of pressure on jugular compression, and after withdrawal of 6 c.c. of fluid the pressure dropped to 0. Protein, 0·075 per cent.; cells, less than 1 per c.mm. After the lumbar puncture there was

recurrence of the sensation of soreness in the right scapular region that had been prominent some months before. No change occurred in the amount of paresis of the lower limbs.

Diagnosis—It was clear that there was spinal compression at the fifth thoracic level, but whether the tumour was within or without the cord was more difficult to decide. The presence of pain in the right side—at first posterior, then in addition anterior, and finally around the chest on that side over a fairly narrow zone associated with cutaneous tenderness—for six months before paraplegic symptoms began to appear weighed strongly in favour of an extramedullary localization. On the other hand, the fact that cutaneous sensory loss was greatest immediately below the situation of the pain and tenderness, and that it was bilateral and symmetrical, favoured a diagnosis of intramedullary tumour. We finally considered, and, as it proved wrongly, that the evidence indicated an intrathecal tumour outside the spinal cord at the level of the fifth thoracic posterior root on the right side.

Operation.—March 20, 1930. Ether anæsthesia. The first to sixth thoracic spinous processes were removed, but this large exposure subsequently proved to be unnecessary, for the lesion was fully displayed by removal of the third, fourth and fifth and the upper part of the sixth thoracic laminæ. When the dura was opened, the spinal cord presented as a fusiform enlargement about 5 cm. long. At the site of maximum swelling the cord was twice its normal size. It was pale and the vessels over its posterior surface were scanty, in contrast with the appearances above and below. Two delicate adhesions were found between the arachnoid membrane and the posterior surface of the cord. These were divided. The swelling was then aspirated by a fine needle, with negative results. The appearances suggested an intramedullary tumour, but the history, in our opinion, had so strongly favoured the diagnosis of an extramedullary tumour that it was considered unwise to incise the cord until its anterior aspect had been examined. Extramedullary tumours, as Elsberg [6] has pointed out, may sometimes become embedded in the anterior aspect of the cord so as to produce appearances simulating those of intramedullary tumour. The spinal cord was therefore thoroughly rotated to examine its right lateral and anterior aspects. There was no sign of tumour. Accordingly the right posterior column was incised, and at a depth of 0·15 cm. the surface of a cherry-red tumour was exposed (fig. 7). The tumour was circumscribed and, as it showed no signs of extruding itself, it was dissected out. By stroking its surface with pledgets of cotton-wool and with the points of fine dissecting forceps it was gradually freed, for it was but lightly adherent to the surrounding cord. As in Case 1, the upper end of the tumour presented a conical depression, and when this was tilted out a small amount of clear fluid came away from what was probably the dilated central canal of the spinal cord. The anterior surface of the tumour was rather more adherent than the rest, and at its centre

was anchored to the spinal cord by a band of firm tissue, subsequently shown to contain numerous arterioles and veins. This was divided between silver clips (fig. 8). The tumour was then easily freed. In order to facilitate removal of its lower part, it was transsected below its centre and the upper part removed. The lower part was less adherent to the cord than any other part of the tumour.

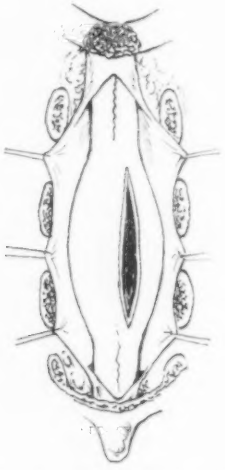


FIG. 7.—*Case* 2. Diagram of operation.

FIG. 8.—*Case* 2. Diagrammatic sketch of tumour being tilted out of the cord, showing vascular pedicle on anterior aspect of tumour. A silver clip has been placed on the pedicle.

The consistence of the tumour was firmer than in Case 1, and the position of the tumour during its removal could thus be controlled by dissecting forceps, without recourse to silk sutures. When the tumour had been removed, its bed appeared as a deep vertically directed cleft in the posterior aspect of the cord, covered by a film of blood-clot. Although the tumour measured over 2 cm. in its widest diameter, the groove was no more than 0·5 cm. wide, and it

seemed remarkable that such a large tumour could have come out of this area.

The situation of the tumour, as shown by subsequent skiagrams of the silver clips which indicated the central point of the tumour, was in the third, fourth and fifth thoracic segments of the spinal cord. The tenderness that had been elicited by palpation of the spine before operation was immediately above the level of the tumour.

While the wound was being closed the pulse-rate rose above 170 and the blood-pressure could not be registered at the brachial artery. The patient became cyanosed and her extremities cold. A blood-transfusion was given, but there was no immediate improvement of her condition, and we formed the impression that the symptoms were not due to secondary anæmia but to manipulation of the spinal cord. The loss of blood during the operation had not been excessive.

FIG. 9.—*Case* 2. (*a*) Tumour after removal. (*b*) Transverse section of tumour showing central cavity.

Pathological examination.—S. D. 678, 1930.—The tumour measured 4·5 cm. long and up to 2·2 cm. in transverse diameter (fig. 9). It weighed 5·6 grm. after twenty-four hours' fixation. Its upper end presented a conical depression, 0·4 cm. deep. The lower end narrowed rapidly to a sharp point. The surface of the tumour was smooth, but to it were adherent a few delicate strands of tissue. These, it was thought, might consist of nerve-fibres, but histological examination revealed no normal nervous tissue. On its anterior surface there was a smooth shallow slit-like depression, 1·1 cm. long. The tumour was composed of greyish-white glistening tissue in which were numerous areas of hæmorrhage. Sections showed a transversely placed cleft, 1·2 cm. wide and 0·2 cm. in an antero-posterior direction, which was continued upwards to open on the surface at the apex of the conical depression in the upper end of the tumour. There was a second and separate cleft, 0·5 cm. wide,

in the lower part of the tumour. Histological examination showed an ependymal glioma (Plate III, fig. 10). No trace of ependymal epithelial lining could be found in the clefts. Their walls were formed by the tissue of the tumour.

Comment.—As will be seen from the notes that follow, the result in this case has not been so far as satisfactory as in Case 1. This may be due in part to the fact that the mid-thoracic cord, being smaller than the cervical cord, is more likely to be seriously injured by operative interference. We feel, however, that the main reason lies in the fact that during the operation the cord was freely rotated for examination of its right antero-lateral aspect. Though rotation of a normal cord can be accomplished without any subsequent disturbance of spinal function, the same procedure must surely be more dangerous when the fibres of the cord are already tightly stretched over an intramedullary tumour. In this case the great delay in recovery of the right lower limb was almost certainly due to damage of the right pyramidal tract during rotation of the cord.

The operation was done in one stage mainly because the patient was so very heavy and obese, not a suitable subject for multiple operations. Moreover, her condition throughout the removal of the tumour, as indicated by five-minute records of the blood-pressure, pulse and respiration rates, did not at any stage indicate that the operation should be abandoned.

Post-operative course.—The general condition of the patient rapidly improved and gave no anxiety. The temperature did not rise above 101° F. However, it was at once evident that there was serious disturbance of spinal function. There was complete paralysis and loss of sensibility in her lower limbs, loss of knee- and ankle-jerks, and retention of urine. She felt that her lower limbs were in a position of acute flexion. Flexor and extensor spasms of the lower limbs were more numerous than before operation.

Recovery of voluntary power.—On the third day after operation very feeble voluntary movements of the left hip and knee were first observed. For several days, however, these movements could only be performed at times and were immediately fatigued, and it was not until nearly three weeks after operation that the patient could voluntarily raise her left knee from the bed. One week later slight voluntary movements began to return in the right lower limb, consisting of adduction and extension at the right hip-joint. Voluntary flexion of the right knee was first observed eight weeks after operation; it was not until three weeks later that there was any voluntary movement of the toes of the right foot. She stood by herself and walked a few steps with assistance for the first time twelve weeks after operation. Movements of the left lower limb were by this time fairly good, but movements of the right lower limb were still feeble and inco-ordinate, and the limb was very spastic. In walking

there was great inversion of the right ankle, and to prevent this a light walking iron was applied. The patient was discharged from the nursing home on June 29, 1930, fourteen weeks after operation. For some months she made very little progress with walking, but when last seen, nine months after operation, she was able to walk fairly well with sticks and was beginning to walk a little without them. She had resumed the management of the house and carried out all indoor activities unaided, but she still preferred to make her outdoor journeys in a wheel-chair. Doubtless her great weight, and also a want of effort, retarded her recovery. Examination at this time showed that voluntary power and tone of the left lower limb were normal, but there was still great weakness of flexion of the right lower limb which was very spastic. Her abdominal muscles recovered first on the left side, but subsequently the right side of the abdominal wall became just as strong.

Recovery of reflex function.—Immediately after operation all the reflexes below the level of the lesion were absent, but within twelve hours an extensor plantar response was obtained on each side, more active on the left than on the right side. These became more brisk in the next twelve hours and at the same time flexor and extensor spasms of the lower extremities began to occur. A feeble right knee-jerk could be obtained on the third day after operation, and the left knee-jerk was first elicited on the following day. These reflexes became quite brisk in the next four days. The right ankle-jerk was first observed three weeks and the left ankle-jerk five weeks after operation. Later the tendon-jerks of the lower limbs became exaggerated, especially on the right side, where there was also sustained ankle clonus. Five weeks after operation the spasms were mostly extensor in type and mainly limited to the right lower limb. These spasms subsequently increased, but were partially controlled by luminal. Fourteen weeks after operation they became less frequent and within two weeks had practically disappeared. The left upper abdominal reflex was first observed fourteen weeks after operation. When the patient was last seen nine months after operation the abdominal reflexes, with the exception of the right upper abdominal reflex, were all present. The plantar reflexes were extensor, and there was also a flexion reflex of the left lower limb which could be elicited by any nocuous stimulation on the left side below the tenth thoracic level. The right knee- and ankle-jerks were exaggerated and sustained clonus could be evoked at the right ankle. The tendon-jerks of the left lower limb were brisk.

After the operation there was complete retention of urine, for which a catheter was passed every six hours. On the seventh day the patient could feel the catheter and became conscious of the filling and emptying of her bladder. On the ninth day she had a violent pain and a sensation of fullness in the region of the bladder. Although the bladder had been supposedly emptied by catheter three hours before, 22 oz. were now drawn off and the urine was offensive and contained pus and bacteria. The discomfort lasted only a few hours, but the urine remained turbid for some days. The patient passed small amounts of urine naturally for the first time three weeks after

operation. Voluntary micturition gradually improved so that two months after operation the amount passed naturally exceeded the amount obtained by catheter. Five months after operation the residual urine had diminished to 2 to 3 oz. Catheterization and bladder washes were stopped shortly afterwards. Nine months after operation the residual urine was less than 1 oz., the frequency was normal and there was no urgency or incontinence. The urine, however, still contained pus and bacteria.

During the first days of convalescence the bowels were moved daily by enema, given while the patient was on a bedpan, for she had no control of the rectal sphincters. She began to regain control of defæcation for the first time about four weeks after operation, and from then on she steadily improved in this respect and was soon better than she had been before operation. On discharge from the nursing home there was no incontinence or urgency of defæcation, and the constipation from which she had suffered before operation was no longer present. The indigestion also did not return.

Recovery of sensation.—Immediately after operation there was complete sensory loss in the lower limbs. Twelve hours later pin-prick could be appreciated on the legs as a touch, but then for a few hours anæsthesia became once more complete, possibly as a result of œdema of the spinal cord at the site of operation. On the third day after operation there was complete cutaneous anæsthesia of the trunk, and some cutaneous analgesia over both lower limbs, especially the left, where there was also gross loss of tactile localization.

Subjective sensory disturbances were prominent. In the first two days after operation the patient felt a warm, tingling sensation in both groins and in the right heel. On the fourth day she began to have fairly severe pain behind the right shoulder and examination showed a zone of severe cutaneous tenderness in the second to fourth thoracic segmental areas on the right side and the second to fifth segmental areas on the left side. Both pain and cutaneous tenderness were more intense on the right side. The pain was aggravated by spasms of the lower limbs. It decreased considerably in severity after five days, but persisted in slight degree on the right side for some months, and then disappeared. The cutaneous tenderness disappeared ten days after operation.

The recovery of sensation was much slower than in Case 1, and it also differed in presenting some disparity between the two sides, which we attribute to injury of the right antero-lateral tract and posterior column at operation. The ability to appreciate and localize pin-prick, heat and cold returned first in the right lower limb, while recovery of postural sensibility and appreciation of light touch returned first on the left lower limb. Of all sensory qualities light touch was the first to recover. Recovery of painful and thermal sensibility occurred first in the sacral dermatomeres and advanced in a headward direction: and during recovery there was some dissociation at the lower limits of sensory loss where pin-prick was appreciated before heat, and heat before cold. On several occasions inversion of temperature sense was observed at both the

upper and lower limits of sensory loss, cold being felt as hot over the fifth and sixth thoracic segments and the lower lumbar segments on the right side. There was no evidence of recovery from the upper limit of sensory loss in a caudal direction.

The first sign of return of postural sense in the lower extremities was observed five weeks after operation when the patient began to recognize the direction of passive movements of the left knee. In the next nine weeks there was no appreciable improvement of postural sense in the lower limbs, but when the patient was again examined six weeks later; that is five months after operation, a great improvement was observed. The direction of movements of the left knee and of most movements of the left ankle was now recognized. At this time there was no recognition of the direction of movements in the right lower limb.

When the patient was last examined nine months after operation there was anæsthesia to cotton wool from the sixth to eleventh thoracic segmental areas, complete analgesia to pin-prick from the fifth thoracic to first lumbar segmental areas and relative analgesia from the first to third lumbar segmental areas. Below this level pin-prick was still appreciated better on the right than on the left side. The loss to heat extended from the sixth thoracic to the fourth lumbar segmental area on the left side and to the fifth lumbar segmental area on the right side; loss to cold from the sixth thoracic to the first sacral segmental area on the left side and to the fifth lumbar segmental area on the right side. Passive movement and position were recognized at all joints of the left lower limb, but no improvement had occurred in the right lower limb. There was still complete inability to recognize written numbers below the fifth thoracic segmental level.

One week after operation a lumbar puncture had been performed as we felt that it was particularly desirable to know at that stage whether there was a likelihood of multiple tumours. The resting pressure was 210 mm. of cerebro-spinal fluid. On jugular compression the pressure rose rapidly to 300 mm. and there was a similar abrupt fall to 200 mm. when pressure on the jugular veins was released. It was thus clear that there was little likelihood of a second tumour.

Pathology.

We do not propose to consider in detail the histology of ependymal gliomas. In our cases the tumours were composed of leashes of cells possessing tails that radiated towards connective tissue trabeculæ and vessels. The cells had no footplates, and specific stains showed that they contained blepharoplasten and fibrils. Both tumours were undoubtedly ependymal gliomas. They were quite circumscribed, but histological examination showed no capsule of connective tissue; instead, the tumours were bounded by a layer of compressed fibrillary

neuroglia. Reticulum was limited to the blood-vessels, which were most numerous in the superficial parts of the tumours.

At operation that part of the spinal cord which contained the tumour presented a fusiform swelling, and in Case 1 there was slight bluish and yellow discoloration of the posterior columns at the site of maximum swelling. Each tumour was connected with the surrounding spinal cord by delicate strands of tissue which could be easily broken at operation by dissection with moist pledgets of cotton wool, or with the points of dissecting forceps. Presumably, these strands of tissue were neuroglia. In Case 2, inspection of the outer surface of the tumour after operation suggested that on it might be some fragments of nervous tissue; however, histological examination showed no nerve fibres but only neuroglia. Sections of necropsy material suggest that there is no serious risk of removing nerve fibres during careful surgical dissection of one of these tumours; around the tumour a zone of gliosis is commonly found and where such a zone is absent the adjacent white matter appears to have undergone degeneration.

Each of these tumours contained one or more cavities, but, whereas in Case 1 the large cavity was lined by ependymal epithelium, in Case 2 the cavity had no such lining, but only walls of tumour tissue. A vascular pedicle was found on the anterior aspect of the tumour in Case 2, and this appears to have provided the main blood supply of the tumour, also the only point of firm attachment. No vascular pedicle was found in Case 1.

Our observations at operation suggest that the tumour extends mainly in a downward rather than in an upward direction, for we found in both cases that the tumour was narrowest, softest and least adherent at its lower end. In each case the upper pole of the tumour presented a depression resembling the uterine cervix in miniature and this portion of the tumour was quite free from attachment to the adjacent spinal cord; and when, during the process of dissection, it was tilted out of its bed, a small amount of clear fluid escaped from the interior of the spinal cord above it. There was no justification for investigating further at operation the reasons for this depression at the apex of the tumour, but the most reasonable inference is that it was produced by fluid under pressure in the dilated central canal of the spinal cord. It is probable that an intramedullary glioma of this type may obstruct the downward flow of cerebrospinal fluid in the central canal of the spinal cord and so produce a slight degree of hydromyelia in those spinal segments that lie immediately above the tumour (fig. 11). Post-

mortem investigations of spinal cords containing ependymal gliomas would help to settle this point. In this connection it is interesting to note that Kronthal [12] found dilatation of the central canal in dogs after gradual compression of the spinal cord.

It is important to recognize that ependymal gliomas of the spinal cord may be multiple or may be associated with syringomyelia in other parts of the spinal cord [11]. When multiple there may also be tumours of the nerve roots of the spinal cord. There are several examples of these combinations in the records of the Pathological Institute of the London Hospital and these are being made the subject of further study.

FIG. 11.—Diagram of intramedullary ependymal glioma to show the depression found in the upper pole of the tumour, and the slight hydromyelia which appeared to have been present above the lesion.

SYMPTOMATOLOGY.

There is no need to stress the desirability of accurate diagnosis before operation in cases of this type. Failure to make this in Case 2 limited considerably the success of the post-operative result, though probably with greater experience of the appearances of spinal tumours at operation the second mistake, of not at once recognizing from the appearances presented that the tumour undoubtedly lay within the cord, may in future be avoided. These cases presented certain similarities of symptomatology, of which girdle sensations below the level of the lesion and numbness of the perineum may be worthy of note. It is in their contrast, however, that their main interest lies. In Case 1, pain was a relatively insignificant symptom and was referred to the back of the neck at the level of the tumour; in Case 2, on the other hand, pain of great severity confined to the right fifth thoracic segmental

area was the only symptom complained of by the patient for the first six months of her illness. Pain is a fairly common symptom of intramedullary tumours, but the occurrence of such a severe radicular type of pain is not a well-known phenomenon. Foerster [8] has observed it in several cases and Schultze [15] has also reported a case in which it dominated the clinical picture. It appears from the literature that it is most likely to appear with intramedullary tumours in the thoracic portion of the cord. Similar pain has been frequently observed by Wilfred Harris [10] in the initial stages of intramedullary gliosis "before any muscular wasting or even before analgesia or thermanæsthesia can be detected." and Foerster [8] has described a remarkable case in which, through a period of years, gliosis gradually spread through one side of the lower cervical cord, segment by segment, producing successively in the corresponding segmental area first hyperalgesia and spontaneous pains, and then analgesia with relief from pain. There is little doubt but that irritation of the region of the posterior horn can produce a pain that in every way resembles "root" pain, and in this connection it will be recalled that Dusser de Barenne [4] has shown that the application of strychnine to the posterior horns in an animal causes very definite paræsthesia in the skin corresponding to the segment of spinal cord that is excited, even after degeneration of the corresponding posterior root. This, however, may not be the invariable explanation of pain like that noted in Case 2. Foerster [8] considers that in some of his cases of intramedullary tumour the "radicular" pain was due to associated adhesions of the arachnoid ("arachnitis"). In our Case 2, two adhesions were found at operation between the posterior surface of the cord and the overlying arachnoid, but these were so delicate, and were moreover so nearly situated in the mid-line, that it is unlikely that they were responsible for the right-sided neuralgia. A thorough examination of the right lateral aspect of the cord was made and no other adhesions were found. We believe, therefore, that the pain in Case 2 was not due to arachnoideal adhesions, but was of intramedullary origin.

The physical signs of intramedullary tumours are probably of more value in diagnosis than the symptoms, though none of them when taken singly may be considered pathognomonic. Attention should be directed rather towards the *combinations* of physical signs that are suggestive of an intramedullary tumour. Signs of a lesion of considerable longitudinal extent in combination with dissociated sensory loss in the areas supplied by the affected segments are suggestive of an intramedullary

tumour. This combination occurred in Case 1, where the lesion evidently extended from the fourth cervical segment (the upper limit of sensory loss) to the first thoracic segment (the lowest limit of observed atrophic palsies). In the parts supplied by these segments there was loss of sensibility to pain, heat and cold with preservation of sensibility to light touch and passive movement; below these segments there was complete sensory loss except in the sacral areas.

In the presence of incomplete sensory loss in the lower limbs, an area of anæsthesia, or of severest sensory loss, on the trunk, which extends up to the region of pain and cutaneous tenderness, suggests an intramedullary lesion. This combination of signs occurred in Case 2.

Severe tonic spasms of the lower limbs at a time when the disturbance of the pyramidal tracts is incomplete is regarded by Foerster [9] as a fairly common sign of intramedullary tumour. This combination of signs was present in each of our cases.

Lumbar puncture yielded yellow cerebrospinal fluid in both our cases and Queckenstedt's test demonstrated a blockage of the subarachnoid space. In Case 1 there was severe aggravation of the symptoms after lumbar puncture, but in Case 2 only slight change followed lumbar puncture. In each case complete relief of blockage of the subarachnoid space was effected by removal of the tumour, as was shown by lumbar puncture after operation.

The Effects Produced by Removal of Intramedullary Tumours.

In both our cases removal of the tumour was followed by tachycardia, but in Case 1, at least, it was no more than the usual reaction that follows cervical laminectomy, for an exactly similar tachycardia had been observed after the first operation when, except for attempted aspiration with a fine needle, the cord itself was not interfered with. Tachycardia after laminectomy is a reaction that needs closer study. From our experience we believe that it is not due to hæmorrhage and this is borne out by Case 2, in which blood transfusion had not the slightest effect of slowing the pulse-rate or in other ways improving the patient's condition. In Case 1 on both occasions the reaction, an abrupt rise of pulse-rate from 120 to 170, occurred *after* the conclusion of the operation and coincided with the recovery from ether anæsthesia.

Records of the blood-pressure were made at intervals of five minutes during the operations, and they did not show any sudden fall of pressure

such as de Martel [13] has observed during manipulation of the cord. In neither case was there any severe rise of temperature after removal of the tumour. In Case 1 the rectal temperature rose to 99·4° F., in Case 2 to 101° F.

It is interesting to observe that in Case 1 the removal of tumour tissue as high as the fourth cervical segment was not attended by any serious respiratory disturbance, for it has been stated [6] that there is danger of sudden death from paralysis of the phrenic nerves during intramedullary operations at this level. In our case the upper pole of the tumour was very loosely connected with the spinal cord and, apart from the incision in the left posterior column, only the gentlest dissection was necessary to enable this part of the tumour to be tilted out. During this stage of the operation the respiration rate rose from 25 to 30, but subsequently fell again.

Interference with the cervical cord in Case 1 produced temporary increase of the ptosis, enophthalmos, and miosis observed before operation, and thus evidently gave rise to increased disturbance of the central connections of the cervical sympathetic. No disturbance of sweating was observed. In a case of angioma within the first thoracic segment operated on by Garrè, Schultze [15] reports that there was profuse sweating of the whole of the patient's face, with the exception of the chin, during the operation.

The only other effect observed from incision of the cervical and upper thoracic cord in Case 1 was severe ataxia of the left upper limb. The incision, it will be recalled, was made through the left posterior column. This ataxia cleared up within a few hours and thereafter no abnormality of the function of the posterior columns could be detected in the upper limbs. It is to be noted also that in this case there was no disturbance of micturition from incision of the cord.

Foerster [8] has observed hyperalgesia, pains and paræsthesias after incision of the posterior columns. Thus, in a case of intramedullary cyst of the cervical cord an incision was made in the right column of Goll of the third and fourth cervical segments, and afterwards hyperalgesia was found in the right lower limb and right half of the abdomen up to the level of the xiphisternum, and the patient complained at times of severe paræsthesias and pains in the hyperalgesic area. No such striking symptoms occurred in our cases. In Case 1, in which the left posterior column was incised from the fourth cervical to the third thoracic segment, there was complete freedom from unpleasant sensory phenomena of this type after operation. In Case 2, in which

the right posterior column was incised from the third to fifth thoracic segment the patient complained twenty-four hours after operation of a warm tingling feeling in both groins, and a sensation in the right heel which she described as "a mixture of pain and normal sensation." These disappeared in a few days. On the fourth day after operation she complained of pain in the right shoulder and was found to have a zone of cutaneous tenderness which extended on the right side, where it was extreme, from the second to fourth thoracic, and on the left side from the second to fifth thoracic segments. This cutaneous tenderness disappeared after a few days leaving very slight relative analgesia. The pain also became much less, but still recurred on occasions for several months.

This zone of cutaneous tenderness corresponded almost exactly with the level and extent of the incision in the cord, but cannot be ascribed to incision of the right posterior column about 1 mm. from the middle-line. It is much more likely to have been due to irritation of the posterior horns themselves and to have been of the same order as the neuralgic pain in the right fifth thoracic segmental area that was such a prominent feature of the early stages of the illness. It is curious, however, that this zone should have occurred at a higher level than the original neuralgic pain. It appears from the history and from the physical signs when the patient first came under our notice that before operation spontaneous pain was severe and cutaneous tenderness slight, whereas after operation pain was not severe but cutaneous tenderness was very acute.

Recovery after the Removal of Intramedullary Tumours.

These cases show that a considerable degree of recovery of spinal function may be expected after the removal of circumscribed intramedullary tumours. As the case reports show the recovery is essentially gradual: it was still progressing in Case 1, when the patient was last examined twenty-two months after operation. The function of the posterior columns below the second thoracic level, which had been completely lost before operation, did not show any sign of recovery until six months after operation, and it was still improving when the patient was last examined.

All forms of sensation recovered in an upward direction, though in Case 1 there was also slight recovery at the upper limit of sensory loss in a caudal direction. Case 2 is of little value in analysing the recovery of sensory function, for this is not as yet sufficiently advanced and the

observation is marred in this, as in other respects, by injury of the right side of the cord during the operation. Case 1, however, shows several points of interest. In this case the recovery of sensibility to cotton wool, pin-prick, heat and cold was rapid in the lower limbs and lower part of the trunk, and much slower and incomplete in the upper part of the trunk. On one occasion the area of anæsthesia to light touch, which before operation had extended up to the second thoracic level, was found to have resolved into two separate areas, an upper area from the second to ninth thoracic segmental areas, and a lower area which extended from the eleventh thoracic to the lower lumbar areas. Subsequently the lower area disappeared completely and rapidly, while the upper disappeared much more slowly. The anæsthesia in distal parts was clearly due to pressure on the long afferent tracts. Observations before operation, though incomplete, suggest that it appeared at a relatively late stage of development of the tumour. During recovery painful stimuli were appreciated before heat, and heat before cold.

Recovery of voluntary power after removal of the tumours occurred in the extensor muscles before the flexors. Reflex function distal to the lesion was temporarily depressed in Case 1, and temporarily abolished in Case 2, after removal of the tumour. Trophic changes in the paralysed parts were very slight before operation, but in both cases after removal of the tumour there was distinct evidence of improvement, as judged by the condition of the toe-nails, which became less brittle and grew more freely.

Treatment.

Successful results from the removal of intramedullary tumours at operation have been reported by Eiselsberg and Ranzi [5], Elsberg [6], Foerster [8, 9], and others, but the modern tendency appears to be towards more conservative measures, either operation by the method of extrusion, or X-ray treatment. From experience with these two cases we wish to urge that operative enucleation of the tumour has its place in the treatment of at least some cases of intramedullary tumour. In our opinion the method advocated by Elsberg and Beer [7] and known as the method of extrusion is not suitable for cases of the type we have described, for from observations at operation it was clear that these tumours would not have extruded themselves appreciably, as they were connected to the surrounding cord by numerous glial adhesions. Some intramedullary ependymal gliomas may be so soft that they can be removed by suction without any damage to the cord, as in a case

reported by Cushing [2], but in our cases suction was found to be ineffective and we feel that the subsequent course of both patients has demonstrated that removal of the tumour by gentle dissection was the most suitable method of attack. Furthermore, perusal of Elsberg's own cases [6] shows that his most successful result, in a tumour closely resembling that of Case 1, was obtained by almost the same methods that we have followed. We feel that there have perhaps grown up around this "method of extrusion" misconceptions that were not originally intended by Elsberg himself. The method doubtless has its uses, but not for all cases of intramedullary tumour.

In a recent monograph Jonesco-Sisesti [11] recommends that treatment should be by means of X-rays, with or without a preliminary decompressive laminectomy. This author has collected nineteen cases of intramedullary tumour associated with syringomyelia and he affirms that surgical removal of the tumours is not practicable, but that X-ray treatment is followed by remarkable success. Bailey and Bucy [1] have also reported considerable improvement in a case resembling our Case 1 after decompressive laminectomy and X-ray treatment. It is difficult for us to compare our cases, in which, of necessity, only a limited examination of the cord was made, with those of Jonesco-Sisesti. He implies that all intramedullary tumours are associated with syringomyelia. It seems fairly well established that syringomyelia may be present above an intramedullary tumour without giving rise to any symptoms, and, though in our cases the clinical course of the disease was rather more rapidly and steadily progressive than in most of the cases described by Jonesco-Sisesti, it is not possible for us to be certain that they do not belong to the group he describes. In any event we feel that the claims he has made for X-ray treatment as opposed to surgical removal of the tumour are by no means fully established, especially in the light of the case of Dowman and Smith [3], in which at successive operations a syringomyelic cavity was evacuated and an intramedullary ependymal glioma was removed, with complete success. The best method of treatment of the various types of intramedullary tumour must for the present remain an open question.

Summary.

Two cases of intramedullary ependymal glioma of the spinal cord are described. In one the tumour extended from the fourth cervical to third thoracic segments; in the other from the third to fifth thoracic segments. Both tumours were completely removed at opera-

tion with good result. The clinical features of the cases, which differed greatly in symptomatology, are discussed and the immediate effects of operation and results of treatment are reported in detail.

LITERATURE.

[1] Bailey, P., and Bucy, P. C. "Tumours of the Spinal Canal," *Surg. Clin. N. Amer.*, 1930, **10**, 233.

[2] Cushing, H. "The Intracranial Tumours of Preadolescence," *Amer. Journ. Dis. Child.*, 1927, **33**, 551.

[3] Dowman, C. E., and Smith, W. A. "Intramedullary Cyst of the Spinal Cord associated with a Circumscribed Intramedullary Tumour," *Arch. Neurol. and Psychiat.*, 1929, **21**, 583.

[4] Dusser de Barenne, J. G. "Strychninwirkung auf das Zentralnervensystem," *Folia Neuro-biol.*, 1913, **7**, 549.

[5] V. Eiselsberg, A., and Ranzi, E. "Ueber die Chirurgische Behandlung der Hirn- und Rückenmarkstumoren," *Arch. f. klin. Chir.*, 1913, **102**, 449.

[6] Elsberg, C. A. "Tumours of the Spinal Cord." London: H. K. Lewis and Co., 1925.

[7] Elsberg, C. A., and Beer, E. "The Operability of Intramedullary Tumours of the Spinal Cord," *Amer. Journ. Med. Sci.*, 1911, **142**, 636.

[8] Foerster, O. "Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände." Berlin: Urban and Schwarzenberg, 1927.

[9] *Idem.* "Zur Diagnostik und Therapie der Rückenmarkstumoren," *Deut. Zeitschr. f. Nervenheilk.*, 1921, **70**, 64.

[10] Harris, Wilfred. "Sensory Changes in Spinal Cord and Medullary Lesions," *Brain*, 1927, **50**, 399.

[11] Jonesco-Sisesti, N. "Tumeurs médullaires associées a un processus syringomyélique." Paris: Masson et Cie., 1929.

[12] Kronthal, P. "Zur Pathologie der Höhlenbildung im Rückenmark," *Neurol. Centralbl.*, 1889, **8**, 633.

[13] de Martel, T. "Le traitement opératoire des tumours de la moelle et de ses enveloppes," *Rev. Neurol.*, 1923, **39**, 701.

[14] Riddoch, G. "The Reflex Functions of the Completely Divided Spinal Cord in Man, Compared with those Associated with Less Severe Lesions," *Brain*, 1917, **40**, 264.

[15] Schultze, F. "Weiterer Beitrag zur Diagnose und operativen Behandlung von Geschwülsten der Rückenmarkshaute und des Rückenmarks, *Deut. med. Woch.*, 1912, **38** (**2**), 1678.

A CONTRIBUTION TO THE NEUROPHYSIOLOGY OF THE URINARY BLADDER IN MAN.

BY JAMES R. LEARMONTH, CH.M.GLAS., F.R.C.S.ED.

(From the Division of Surgery, The Mayo Clinic, Rochester, Minnesota.)

CONTENTS.

PAGE

INTRODUCTION 148

PART I.—THE PHYSIOLOGICAL ANATOMY OF THE NERVES OF THE BLADDER .. 148

PART II.—OBSERVATIONS ON THE INNERVATION OF THE BLADDER 154

(I) The exstrophic bladder :—
- (1) Effect of contraction of the interureteric muscle on the ureteral orifices.
- (2) Effect of intravenous injection of adrenaline on the exstrophic bladder.

(II) Results of faradic stimulation of the sympathetic nerve supply in the intact bladder :—
- (1) The presacral nerve.
- (2) Either hypogastric nerve.
- (3) A lateral root of the presacral nerve.
- (4) Central end of cut presacral nerve.
- (5) Central end of one cut hypogastric nerve, the other being intact.

(III) The immediate results of division of the sympathetic nerves of the bladder.

(IV) The late results of division of the sympathetic nerves of the bladder.

(V) The effect of intravenous injection of adrenaline upon the capacity of the bladder.

PART III.—ANALYSIS OF THE VARIOUS IMPULSES CARRIED BY THE NERVES OF THE BLADDER 160

(I) Afferent fibres :—
- (1) Fibres which convey impulses which indicate the degree of distension (as distinguished from over-distension) of the bladder.
- (2) Fibres which convey impulses of pain from the bladder.
- (3) Afferent fibres conveying impressions of tactile and thermal sensibility.
- (4) Afferent fibres concerned in the micturition reflex.

(II) Efferent fibres :—
- (1) Motor fibres to the detrusor muscle of the bladder.
- (2) Motor fibres to the muscle guarding the uretero-vesical orifices.
- (3) Motor fibres for the trigonal muscle.
- (4) Motor fibres for the internal sphincter of the bladder.
- (5) Inhibitory fibres for the detrusor muscle.
- (6) Inhibitory fibres to the internal sphincter.
- (7) Vasoconstrictor fibres to the vesical arteries.

(III) The segmental levels of the spinal cord associated with the innervation of the bladder :—
- (1) Parasympathetic fibres.
- (2) Sympathetic fibres.
- (3) Somatic fibres.

PAGE

PART IV.—THE PHYSIOLOGY OF THE COMPONENT PARTS OF THE BLADDER .. 169

(I) The detrusor muscle.
(II) The ureteric orifices.
(III) The internal sphincter.
(IV) The blood-vessels of the bladder.
(V) Sensation in the bladder.
(VI) Afferent fibres for the micturition reflex.

PART V.—THE ACT OF MICTURITION. NOTE ON THE INNERVATION OF CERTAIN MALE GENITAL ORGANS 173

INTRODUCTION.

THROUGHOUT this paper the term "sympathetic" will be used to denote that part of the autonomic system which leaves the spinal cord in the thoracicolumbar region, whereas the term "parasympathetic" will be used for the part of the autonomic system leaving the sacral region of the cord.

In the course of surgical operations for the relief of certain vesical conditions, I have had a unique opportunity for making direct observations on the sympathetic control of the urinary bladder. These observations, together with a study of the physiology of the bladder after sympathetic neurectomy, form the basis of this report. By analysing my data, I have been able to clarify certain neurophysiological aspects of vesical function. The paper is strictly confined to the physiology of the human being: it follows that there has been little opportunity for multiplying observations. It is true that in recording the results of observations upon human beings a worker has the great advantage of being able to converse with his subject, so that much may be made of any one opportunity. On the other hand, he cannot make full use of the many instruments of precision available for recording physiological changes during experiments upon animals; nor can he consistently use the fruitful method of degenerative nerve section.

It is a pleasure to record my thanks for the helpful co-operation of my colleagues of the Section on Urology of The Mayo Clinic. On many occasions they have, at my request, consented to subordinate their own interest in the subject by making observations in ignorance of what was being done, or had been done, to the various vesical nerves.

PART I.—THE PHYSIOLOGICAL ANATOMY OF THE NERVES OF THE BLADDER.

It is essential to introduce this section because of inaccuracies in the description usually given in current textbooks of physiology. The majority of the sympathetic nerves for the pelvic viscera, including those

for the urinary bladder, pass through a "bottle neck" in front of the sacrum, where they are collected together as the presacral nerve [10] or superior hypogastric plexus [9]; this forms a convenient point of departure. The presacral nerve has three roots: a right and left lateral, and a middle (fig. 1). On the right side the lateral root begins about 1·5 cm. below the right renal artery, by the union of three or four nerve bundles of constant origin [11]. The most internal arises from a nervous loop which crosses the aorta below the origin of the superior mesenteric artery; the middle springs from the semilunar ganglion or

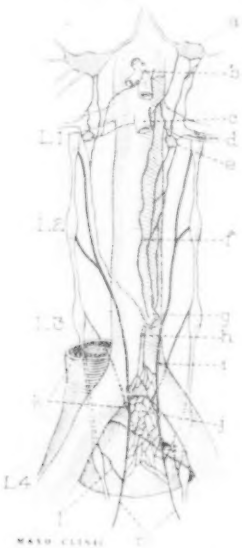
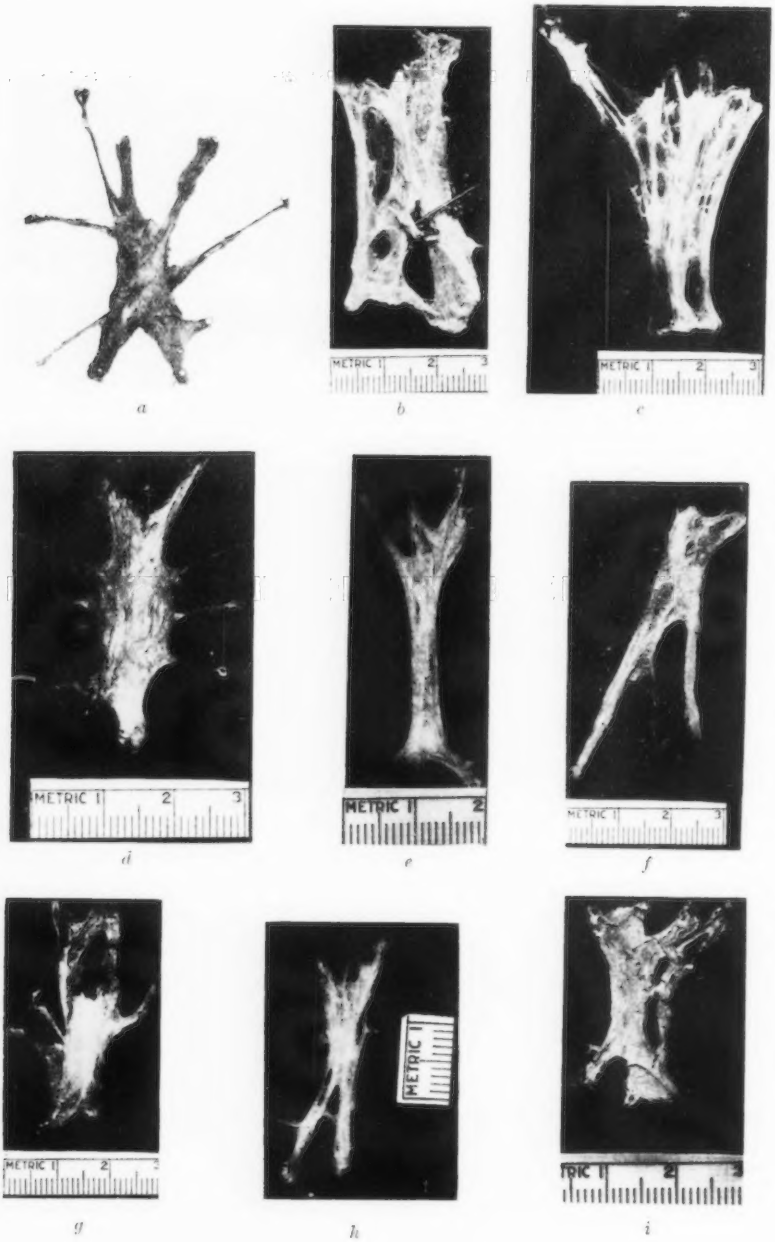


FIG. 1.—Connections of the presacral nerve: (*a*) semilunar ganglion; (*b*) cœliac plexus; (*c*) superior mesenteric artery; (*d*) renal plexus; (*e*) renal ganglion; (*f*) intermesenteric plexus; (*g*) inferior mesenteric artery; (*h*) middle root of presacral nerve; (*i*) left lateral root of presacral nerve; (*j*) presacral nerve; (*k*) branch from third lumbar ganglion; (*l*) branch from fourth lumbar ganglion; and (*m*) hypogastric nerves. (After Laux.)

cœliac plexus, the external from the right periarterial renal plexus; these twigs unite to form a single small filament. As this passes downward it is joined on its outer side by two branches arising from the first and second lumbar ganglia respectively. Most of the fibres of the original root pass to the intermesenteric and inferior mesenteric plexuses; the remainder, with the branches from the lumbar ganglia, continue their downward course and reach the interval between the common iliac arteries as the right lateral root of the presacral nerve.


METRIC 1 2 3
METRIC 1 2 3
METRIC 1 2 3
METRIC 1 2
METRIC 1 2 3
METRIC 1 2 3
METRIC 1
METRIC 1 2 3

a *b* *c*

d *e* *f*

g *h* *i*

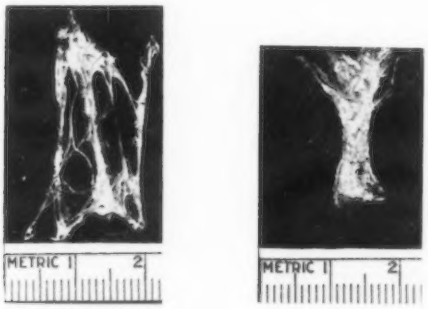


FIG. 2.—Types of presacral nerve: (*a*) above on the right, branches from first and second lumbar ganglia; on the left, these branches are united to form one trunk. On each side are the branches from the third and fourth lumbar ganglia. Below are the two hypogastric nerves; (*b*) the tip of the arrow lies under the union of the branches from the third lumbar ganglia, which enters the nerve posteriorly; (*d*) solid type: (*j*) plexiform pe. Central end of nerve at top.

The left lateral root of the nerve has a similar origin. The middle root is the prolongation downward of the intermesenteric plexuses, after they have supplied the roots of origin of the inferior mesenteric nerves; these intermesenteric plexuses establish wide connections with the cœliac, semilunar and aortico-renal ganglia. The middle root of the presacral nerve is received into the angle of convergence of the lateral roots. The presacral nerve itself is subject to wide variations in form (fig. 2); usually it is stated to be more or less solid in 20 per cent. of cases, and plexiform in the remaining 80 per cent.; however, according to my own experience, these figures should be interchanged. The nerve receives additional communications on each side, from the third and fourth lumbar ganglia; in the specimens which I have examined the branches from the third lumbar ganglia usually united to form a single filament which entered the posterior aspect of the nerve (fig. 2 (*b*)). From a histological standpoint (fig. 3) the majority of the fibres springing from the lumbar ganglia are medullated, whereas the fibres of the middle root are non-medullated; the former make up about 60 per cent. of the total fibres of the presacral nerve, the latter about 40 per cent. A few ganglion cells are to be found in the substance of the presacral nerve; with these some of the nerve fibres from the lumbar ganglia form synapses.

The presacral nerve dips into the pelvis, and about the level of the first part of the sacrum it divides into the two hypogastric nerves

From somewhere in the neighbourhood of this division, a large nerve passes on both sides to supply the lower part of each ureter. Each hypogastric nerve ends in a corresponding hypogastric ganglion, situated on a lateral aspect of the rectum (fig. 4); these ganglia may receive a

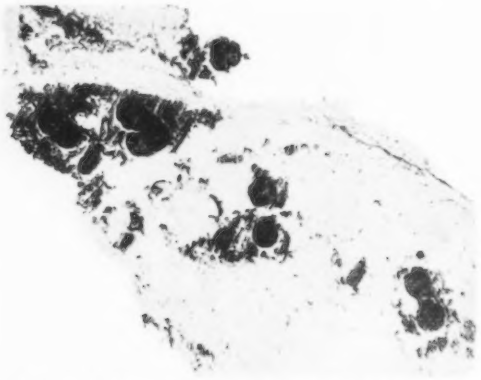


FIG. 3.—Section of presacral nerve, to show fasciculi lying in connective tissue. Stained for myelin, in order to determine the numbers of preganglionic and postganglionic fibres present. (× 15, Weigert's myelin sheath stain.)

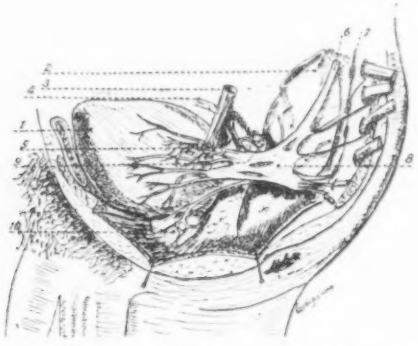


FIG. 4.—Left hypogastric ganglion, lateral aspect: *1*, bladder; *2*, rectum; *3*, ureter; *4*, vas deferens; *5*, vesical nerves; *6*, left hypogastric nerve; *7*, sacral sympathetic chain; *8*, hypogastric ganglion; *9*, seminal vesicle; *10*, prostate gland. The parasympathetic nerves from the second and third sacral nerves to the hypogastric ganglion are also shown. (After LAUX.)

few sympathetic fibres directly from the third and fourth sacral ganglia of the paravertebral sympathetic chains.

The parasympathetic nerves of the bladder are derived from the anterior primary divisions of the second and third sacral nerves on both

sides (fig. 4). They join the corresponding hypogastric ganglia: there are no direct branches from the sacral nerves to the bladder. From the anterior borders of the hypogastric ganglia emerge a dozen or so branches of distribution, the upper branches containing both sympathetic and parasympathetic nerves for the bladder. The question of the situation of the synapses on these autonomic nerves will be considered later. The prostatic urethra and the external sphincter receive somatic fibres by way of the pudic nerves, which spring from the anterior primary divisions of the third and fourth sacral nerves: they do not pass through the hypogastric ganglia.

These intricate connections may now be examined in their broader physiological aspects. In the first place, it is necessary to dispose of the statement that the sympathetic nerves of the bladder are derived from a hypothetical inferior mesenteric ganglion, a mistake that has arisen from too slavish a transference of the arrangement in animals to conceptions of human physiology. It is true that in the human fœtus at the sixth week a definite inferior mesenteric ganglion has been described [6]. Such a structure is by no means constant in the adult: Petit-Dutaillis and Flandrin [16] identified it in five of thirteen subjects: Hovelacque [9] stated that it occurs in 50 per cent. of cases, and I myself have been able to identify it in but one of fourteen cases. Although it may be argued that lack of uniformity is a notorious feature of vesical innervation, and that when the ganglion is present it may play an important part in relaying the nerves to the bladder, on the other hand I shall show that important effects on the musculature of the bladder occur on stimulation of the lateral root of the presacral nerve. As the lateral roots are for the whole of their courses remote from the site of the supposed inferior mesenteric ganglion, I incline to the view that in man this structure has lost the physiological importance which it undoubtedly possesses in many other vertebrates. In the second place, it is well to emphasize the physiological fact that this nervous pathway contains direct connections between the nerves of the kidneys and those of the ureters and bladder. These connections ensure integration of the physiological processes concerned in the formation and the disposal of urine; they provide a pathway which probably co-ordinates the activity of the renal parenchyma, the transmission of urine along the muscular conduit formed by the renal pelvis and the ureter, the storing of urine in the bladder, and its final expulsion from that viscus.

PART II.—OBSERVATIONS ON THE INNERVATION OF THE BLADDER.

(1) *The exstrophic bladder.*—Before an opportunity of directly stimulating the vesical nerves occurred, I was able to settle one or two physiological points by making observations on exstrophic bladders. It may be objected that both the musculature and nerve supply of such a rudimentary bladder are likely to be abnormal: but the nature of the procedures was such that these objections have little weight.

(1) Effect of contraction of the interureteric muscle on the ureteral orifices.—In two cases of exstrophy of the bladder, I was able to pro-

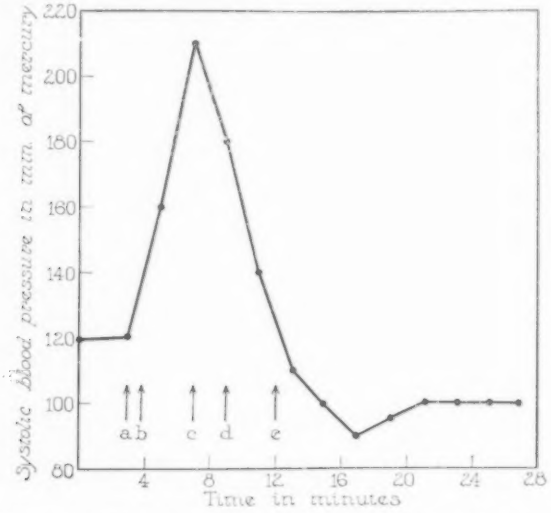


FIG. 5.—Effect of intravenous injection of adrenaline hydrochloride in a case of exstrophy of the bladder: (*a*) intravenous injection of 0·3 c.c. of 1 : 1000 adrenaline hydrochloride; (*b*) blanching and contraction of rudimentary bladder; (*c*) left ureteric orifice opened: four spurts of urine; (*d*) left ureteric orifice closed; (*e*) relaxation of rudimentary bladder.

duce strong contractions of the interureteric muscle by faradic stimulation. I found that the strongest obtainable contractions had no effect on the size or shape of the orifices of the ureters. Indeed, during such contractions it was possible to observe them opening for the expulsion of urine, and closing after the jet of fluid had ceased.

(2) Effect of intravenous injection of adrenaline on the exstrophic bladder.—This was an attempt to determine the action of sympathetic nerves on the trigone and ureteric orifices of the bladder: these are the parts represented in the exstrophy. The patient was an adult, aged 24, whose right ureter had been transplanted to the bowel ten days pre-

viously. A dose was given of 0·3 c.c. of a 1 : 1000 solution of adrenaline hydrochloride, diluted in 5 c.c. of physiological saline solution. The blood-pressure was noted by means of a Pachon's self-recording oscillometer. The effect of the drug is shown in fig. 5. About thirty seconds after the blood-pressure began to rise, the rudiment of the bladder became contracted and blanched; this appearance persisted for about eight minutes. Four minutes after the injection the left ureteric orifice, hitherto contracted, opened widely, and four spurts of urine appeared. After remaining open for two minutes the left ureteric orifice once more closed tightly. The right ureteric orifice remained closed throughout.

Thus the action of adrenaline was to cause contraction of the trigonal region, contraction of the ureteric orifice and increased expulsion of urine.

(II) *Results of faradic stimulation of the sympathetic nerve supply in the intact bladder.*—It has been possible to make direct observations on the nerve supply to the bladder on six occasions. Each of these operations was performed under spinal anæsthesia, which of course leads to paralysis of the sympathetic and parasympathetic fibres leaving the spinal cord as high as the sixth or seventh thoracic segment. Naturally, the paralysis is limited to preganglionic fibres, and the viscera are still under any controlling influences possessed by the peripheral ganglia, whether intrinsic or extrinsic. It may be thought that the use of spinal anæsthesia would obscure the factors to be investigated, but in actual practice difficulty was not encountered in interpreting the findings. Moreover, spinal anæsthesia does not lead to general dulling of nerve fibres and nerve cells throughout the body, as is the case with inhalation anæsthesia. The observations were made in such a way as to preclude the influence of any preconceived ideas; before beginning the research, I prepared a numbered table, showing the tests I desired to make on each part of the sympathetic nerve supply of the bladder.

Stimulation of:—

(1) Intact presacral nerve.
(2) Left hypogastric nerve.
(3) Right hypogastric nerve.
(4) Left lateral root.
(5) Right lateral root.
(6) Central end of cut presacral nerve.
(7) Central end of one cut hypogastric nerve, the other being intact.

When possible, each of these tests was carried out while observations were made on the orifices of the ureters, the trigone, the blood-vessels of the trigone, the internal sphincter of the bladder, the musculature of the prostate gland, and the musculature of the ejaculatory ducts. Each step was referred to by number only, and the observations made by the cystoscopist were recorded under that number: after the conclusion of the operation the results of each step were transferred to the procedure corresponding to the number. The cystoscopist was thus in entire ignorance of what was being done to the nerves.

Since the results obtained in all six cases were identical, I do not insert the protocol of each. The following description is a composite one. The current used was faradic, and the strength of stimulus was that which gave rise to a brisk twitch when the electrodes were applied to an exposed rectus abdominis muscle.

(1) The presacral nerve.—The effects noted were obtained whether the intact presacral nerve was stimulated, or the peripheral end of the divided nerve.

(*a*) Contraction of ureteric orifices. This contraction is a powerful one, the orifices assuming a pin-point appearance. Occasionally the contraction is preceded by the delivery of a forceful jet of urine. When the stimulus is discontinued, the orifices return slowly to the moderate degree of dilatation which is usual under spinal anæsthesia.

(*b*) Increased tonus in trigone. The term increased tonus is used advisedly, rather than contraction. The process appears to be a gradual tightening of the floor of the bladder, which disappears fairly rapidly when the stimulus is discontinued.

(*c*) Contraction of internal sphincter. This contraction has no appreciable latent interval. When the stimulus ceases, it may be about two minutes before the sphincter returns slowly to the moderately relaxed condition which is usual under spinal anæsthesia; however, it may relax at once. If an instrument is introduced through the sphincter, and the nerve is then stimulated, the instrument is grasped so tightly that considerable force is necessary to move it.

(*d*) Contraction of prostatic musculature. This is recognized by the cloud of prostatic secretion which is poured into the posterior urethra when the nerve is stimulated. Naturally it is less easily observed at each succeeding stimulus, as the prostatic glands are gradually emptied.

(*e*) Contraction of the musculature of the seminal vesicles and ejaculatory ducts. This is recognized by the forcible expulsion of semen into the posterior urethra. It is easiest to observe this at the first stimulation of the nerve.

(*f*) Contraction of the blood-vessels of the trigone. This is what might be expected, and is in keeping with the control of blood-vessels elsewhere. It is easy to recognize, since the vessels are previously somewhat relaxed by the action of the spinal anæsthetic.

(*g*) No observable effect on the musculature of the lateral walls and dome of the bladder. This is an important observation, as it sheds light on the mode of action of the inhibitory nerves which the presacral nerve will be shown to contain.

(2) Either hypogastric nerve.—Stimulation of the intact hypogastric nerve, or of its peripheral end after it had been severed from the presacral nerve, resulted in the following :—

(*a*) Contraction of the ureteric orifice on the same side. A contraction of the opposite ureteric orifice has never been noted.

(*b*) Tautening of the trigonal region. It has been impossible to decide whether this is an ipsolateral or a bilateral effect.

(*c*) Contraction of the internal sphincter.

(*d*) Contraction of the prostatic musculature.

(*e*) Contraction of the musculature of the seminal vesicles and ejaculatory ducts.

In short, the evidence at my disposal points to control of a ureteric orifice by the ipsolateral hypogastric nerve, while the internal sphincter and the musculature of the accessory generative organs appear to be affected as a whole by the stimulation of either hypogastric nerve.

(3) A lateral root of the presacral nerve :—

(*a*) Contraction of the internal sphincter.

(*b*) Contraction of the prostatic musculature.

(*c*) Contraction of the musculature of the seminal vesicles and ejaculatory ducts. I have not had an opportunity of observing the effect of stimulation of a lateral root on the ipsolateral ureteric orifice.

(4) Central end of cut presacral nerve. I have never been able to produce any observable reflex effect on the bladder by a stimulus, however strong, applied to the central end of the cut presacral nerve. The pain which is felt during the period of stimulation will be considered in a later section.

(5) Central end of one cut hypogastric nerve, the other being intact.—Effects on the bladder or internal sphincter have not been obtained, either before or after division of the presacral nerve. Thus I cannot present any evidence for the existence of a Sokownin reflex in man.

(III) *The immediate results of division of the sympathetic nerves of the bladder.*—If the presacral nerve is cut above, the two hypogastric

nerves below, and the intervening segment removed so as to free the bladder from all (or almost all) sympathetic influences, the following effects are observed:—

(1) The ureteric orifices, formerly slightly relaxed, become much more open.

(2) The entire trigone appears relaxed.

(3) The internal sphincter becomes much more relaxed.

(4) The blood-vessels of the trigone become widely dilated.

(5) There is no observable change in the dome and lateral walls of the bladder.

(IV) *The late results of division of the sympathetic nerves of the bladder.*—If the bladder is examined after the subject's convalescence, that is, about twenty-one days after the original operation, it will be found to have changed, so that its appearance is nearer the normal.

(1) The ureteric orifices now close in the intervals between each jet of urine.

(2) The trigone appears less relaxed, but still abnormal.

(3) The internal sphincter may close completely. However, it can be easily opened by the advancing beak of the cystoscope, and gives one the impression that it yields more rapidly than normally.

(4) The persistence of any marked degree of vascular dilatation in the trigonal region has not been noted.

TABLE I.—Summary of the Results obtained by stimulating the Component Parts of the Presacral Nerve.

Structure	Nerve			
	Presacral	Hypogastric	Lateral root, presacral	Middle root, presacral
Ureteric orifice	Contraction	Contraction (ipsolateral)	Not done	Not done
Trigonal region	,,	Contraction	..	..
Internal sphincter	,,	,,	Contraction	,,
Prostatic musculature	,,	,,	,,	,,
Musculature of seminal vesicles and ejaculatory ducts	,,	,,	,,	,,
Blood-vessels of bladder	,,	Not done	Not done	,,
Dome and lateral walls of bladder	No effect	No effect	..	..

The significance of the foregoing observations will be considered in the next section. Here it may be emphasized that they furnish the first direct proof that the sympathetic system controls the trigonal

region[1] and internal sphincter in the human being, as well as that they provide the first direct information regarding the innervation of the prostatic musculature and that of the seminal vesicles and ejaculatory ducts. I am conscious that there are deficiencies in the work, which are easily seen by reference to Table I. At an early stage I obtained indirect and collateral evidence which will enable me to offer a strong hypothesis in regard to the functions of the middle root of the presacral sympathetic nerve; therefore, as the opportunities for these investigations are few, I concentrated on obtaining accurate information on the functions of the other components of the nerve.

(V) *The effect of intravenous injection of adrenaline upon the capacity of the bladder.*—On two occasions I have endeavoured, during operation, to establish the presence of sympathetic inhibitory nerves to the vesical musculature by connecting the partially-filled bladder to a manometer and noting the effect of faradic stimulation of the presacral nerve on the intravesical pressure; but I found that a satisfactory technique was nearly impossible in the operating room. Although on both occasions a slight dilatation of the bladder appeared to follow sympathetic stimulation, I did not consider it conclusive, as in both cases the bladder was inflamed, and the increase in capacity not beyond the normal oscillations of pressure.

In order to settle this point, I determined to test the effect of intravenous injection of adrenaline on the capacity of a normally innervated healthy bladder. I myself was the subject of the experiment, the details of which follow. A catheter was introduced into the bladder and connected to a burette by a flexible rubber tube. On the burette was fixed a metric scale. The bladder was then filled with physiological saline solution, tinted with phenolsulphonephthalein, until there was a small head of fluid in the burette. This stage of filling was reached without any vesical discomfort, or any feeling that the bladder required to be emptied. A period of four minutes was then allowed to elapse, during which the level of the fluid in the burette remained constant, save for small respiratory excursions, which amounted to less than one unit volume. The adrenaline was then injected intravenously. To gauge the necessary dose, 0·2 c.c. of a 1 : 1000 solution of adrenaline hydrochloride was diluted with 3 c.c. of physiological saline solution; when 1 c.c. of this mixture had been injected (=0·07 c.c. of 1 : 1000 adrenaline hypochloride), the general effects of the drug became so

[1] Pharmacological evidence on this point has been published by Young and Macht [23].

marked that the injection was stopped. The results of the "chemical sympathetic" stimulation of the bladder are shown in figure 6. The observations of vesical capacity, which are, of course, relative, were made at intervals of twenty seconds, and if possible during expiration. The curve shows that there occurred an immediate active dilatation of the viscus, which remained at its new greater capacity for approximately five minutes. After this interval rhythmic oscillations in pressure appeared, although the mean pressure was maintained for approximately five and a half minutes at a lower level than at the beginning of the experiment. The experiment was terminated when a desire to void was felt.

These findings offer additional evidence that inhibitory fibres to the detrusor muscle of the bladder may be present in the human being.

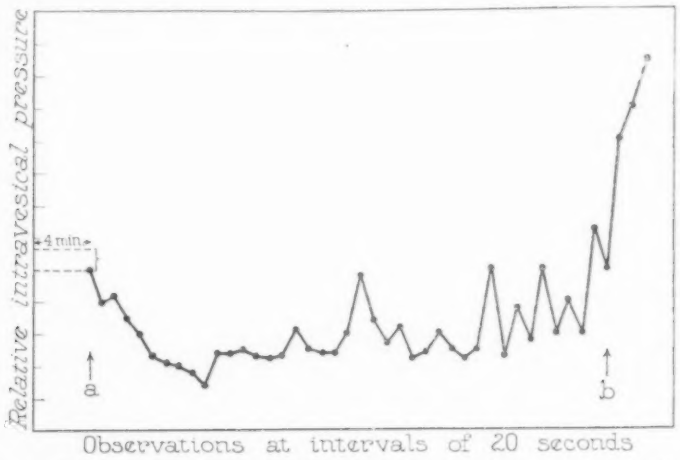


FIG. 6.—Effect of intravenous injection of adrenaline on the capacity of the bladder: (*a*) injection of 0·07 c.c. adrenaline hydrochloride, 1 : 1000 diluted with 1 c.c. of physiological saline solution; (*b*) desire to void.

PART III.—ANALYSIS OF THE VARIOUS IMPULSES CARRIED BY THE NERVES OF THE BLADDER.

In this analysis of the paths followed by the various nervous impulses which reach or leave the bladder, I have made use of evidence from a number of sources. Some has been obtained directly during operations under spinal anæsthesia: the rest has been gathered from observations made after operation, from findings of post-operative cystoscopic examination, from examination of tissues in the post-mortem room, and

from cases published by others—all these have contributed links from which it has been possible to construct a tolerably complete chain. In hominal research this method is almost the only one which can be used, for each problem is so complex that observations on one subject cannot be extended to cover the whole.

(1) *Afferent fibres.*—(1) Fibres which convey impulses which indicate the degree of distension (as distinguished from over-distension) of the bladder. I have elected to consider this aspect of vesical sensation first, because I regard it as the most important in the excitation of the micturition reflex. We have some information on this point from the

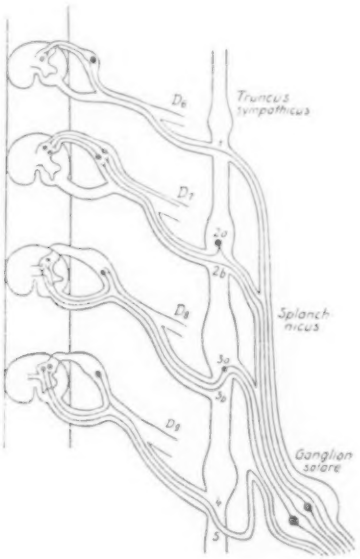


FIG. 7.—Paths by which an afferent fibre from a viscus may enter the central nervous system.

report of Head and Riddoch [8]. One of their patients had had the lower end of his spinal cord destroyed by a wound. Therefore, the only remaining pathway from the bladder to the central nervous system was the sympathetic pathway, which entered the cord above the destroyed segments. Now this patient knew when his bladder filled up, although he was entirely unconscious of its emptying.

The sympathetic pathway contains fibres which convey impulses giving information as to the degree of distension of the musculature of the bladder.

On the other hand, in all the cases, fourteen in number, in which I have had occasion to resect the sympathetic pathway to the pelvic viscera, after operation distension of the bladder has been readily perceived by the patients. In these cases the only available pathway from the bladder to the central nervous system is by way of the pelvic (parasympathetic) pathway, and the second and third anterior primary divisions of the sacral nerves.

The parasympathetic pathway contains fibres which convey impulses giving information as to the degree of distension of the musculature of the bladder.

(2) Fibres which convey impulses of pain from the bladder.—I obtained my first accurate anatomical evidence on this point during the course of an operation, when I had occasion to grasp the presacral nerve (sympathetic pathway) with an artery forceps. When the nerve was pulled the patient complained of pain; after section of the nerve, traction on its central end caused pain. In this case, the effect of the spinal anæsthetic was passing off from above downward, although at the time the observations were made the skin was analgesic as high as the tenth thoracic segment. The impulses necessarily entered the spinal cord above this level, possibly along the roots of the splanchnic nerves. The description of the pain is interesting; it was characterized as "a crushing pain in my bladder." This is a remarkable example of the localization of visceral pain, and is in contrast with the statement of Head [7] that "the pain (of an overdistended bladder) is felt in the twelfth thoracic and first lumbar dermatomes." This patient, because of severe deafness, was quite unaware of the stage which the operation had reached, and thus the evidence is reliable. Even after leading questions he would not admit to feeling any such referred pain. During operation under light general anæsthesia, on several occasions I have seen patients show uneasiness when the central end of the cut presacral nerve was stimulated with a strong faradic current. I have much corroborative evidence from the statements of patients on whom section of the presacral nerve has been performed for painful conditions of the bladder; invariably the vesical pain has been diminished, although not abolished, by this procedure. It must be added, however, that there is no conclusive evidence regarding the stimulus which normally gives rise to such pain; probably, as is the case with other contractile viscera, it is either the overstretching or the spasmodic contraction of the muscle bundles which exercises a mechanical effect on the nerve fibres between them.

The sympathetic pathway contains afferent fibres which convey impulses set up by painful sensations in the bladder.

I have treated one patient, who had a painful condition of his bladder, by dividing the vesical branches of both hypogastric ganglia; thus the bladder was freed from all autonomic connections with the central nervous system. During the eight days in which he survived the operation he was entirely free from all forms of pain in the bladder. At the necropsy, I was able to satisfy myself that the neurectomy had been complete, and also to find an explanation for the pain around the neck of the bladder and in the posterior urethra, which had been part of his complaint. The prostate gland and posterior urethra had been invaded by a malignant growth. It must be concluded, therefore, that fibres using an autonomic pathway at least partly subserve sensation in the posterior urethra. This observation is contrary to the accepted view, which allocates the sensory nerve supply of the posterior urethra to the somatic fibres of the pudic nerve.

The parasympathetic pathway contains afferent fibres which convey impulses set up by painful sensations in the bladder. By this pathway also travel at least a proportion of the sensory nerves of the posterior urethra.

(3) Afferent fibres conveying impressions of tactile and thermal sensibility.—I can offer only indirect evidence regarding the path of the fibres which convey impressions of tactile and thermal sensibility. It is odd that the bladder should possess such fibres at all; however, they appear to be present, and to end especially around the three openings into the bladder [14]. Evidence of their presence in the sympathetic pathway could not be elicited by questioning the patient referred to on this page. On the other hand, it is of great interest that Riddoch's patient was able to tell when a catheter entered his bladder. In the cases in which the condition of the bladder allowed it to be done, estimation of the acuity of the tacto-thermal system after resection of the sympathetic pathway did not reveal any diminution in sensitivity.

The available evidence points to the view that almost all the afferent fibres conveying impressions of tactile and thermal sensibility traverse the parasympathetic system only; a few fibres of this nature, originating about the neck of the bladder, may travel by the sympathetic system.

(4) Afferent fibres concerned in the micturition reflex.—This is, perhaps, the best stage at which to consider the route followed by those

afferent fibres which subserve the micturition reflex; although logically the nature of adequate stimulus should be considered first. This point, as well as the sequence of events in the act, will be taken up later. It must be admitted that the only definite evidence on the question of the path traversed by "reflex" fibres is the fact that, after the first few days following resection of the sympathetic nerves of the normally innervated bladder, micturition is apparently normal. In a certain number of cases, the division of the inhibitory nerves which travel by the sympathetic pathway leads to some frequency; but this phase is transient, and although I have closely questioned the fourteen patients on whom I have performed this operation, I could not discover any evidence of departure from the normal, so far as micturition was concerned.

The sympathetic pathway from the bladder is not essential for the act of micturition. It follows as a corollary that by far the most important path for "reflex" fibres is the parasympathetic system, and ample evidence to support this view is forthcoming from various known diseases affecting the act of micturition, in which the lesion affects some part of the parasympathetic pathway. A detailed consideration of these would be out of place in this paper.

Most, if not all, "reflex" afferent fibres from the bladder reach the central nervous system by the parasympathetic pathway.

II.—*Efferent fibres.*—(1) Motor fibres to the detrusor muscles of the bladder.—So far as I am aware, all the information regarding the motor nerve supply of the detrusor muscle in the human being is derived from study of the effects of injury or disease upon the sacral segments of the spinal cord, the roots of the cauda equina, and the parasympathetic component of the second and third sacral nerves. It is a clinical fact, which need not be laboured in a paper of this nature, that destructive lesions of these parts of the nervous system lead to loss of ability to pass urine voluntarily, together with paresis of the muscular walls of the bladder which can be appreciated with the cystoscope. It is important to emphasize the word paresis used in the preceding sentence; that there is, in such cases, no complete or permanent paralysis of the intrinsic neuromuscular mechanism of the bladder is shown by the subsequent development of a more or less adequate "automatic bladder." Fibres springing from these parts of the central nervous system belong to the parasympathetic system. It has been shown that stimulation of the sympathetic pathway does not lead to any contraction of the detrusor muscle.

The parasympathetic nerves provide motor fibres for the detrusor muscle of the bladder.

(2) Motor fibres to the muscle guarding the uretero-vesical orifices.—I have already provided direct evidence that the ureteral orifices contract on stimulation of the vesical sympathetic nerves.

(3) Motor fibres for the trigonal muscle.—As I have shown, the sympathetic pathway provides motor fibres for the trigonal muscle.

(4) Motor fibres for the internal sphincter of the bladder.—I have shown that the sympathetic pathway provides motor fibres for the internal sphincter of the bladder.

(5) Inhibitory fibres for the detrusor muscle.—Although Elliott [3] has stated that there are no inhibitory nerves to the detrusor of the bladder in the human being, I shall present evidence which appears to put their existence beyond doubt.

(*a*) In the first place, all surgeons interested in this field are aware of the transitory period of frequency of micturition which occasionally follows division of the sympathetic nerves of the bladder. It may be objected that the frequency passes off, so that in a few days no change from the normal can be detected. This objection is reasonable, but by no means insuperable. Many examples are known in which an intact part of the central nervous system takes over the function of a part which has been destroyed.

(*b*) In the second place, I have had the opportunity of following, for one year and for eight months respectively, two cases in which the most reasonable explanation of the operative cure of vesical paralysis is the assumption that the sympathetic nerves of the bladder contain a proportion of inhibitory fibres.

The first of these patients [13] was ideal for the investigation of this physiological problem, because the damage to his central nervous system was easy to define. Briefly, he showed evidence of damage to the second, third, fourth, and fifth sacral segments of the spinal cord, that is, to the segments from which the parasympathetic nerves to the bladder take their origin. He was able to micturate only with great difficulty, and so incomplete was the act that his bladder contained on an average about 300 c.c. of residual urine. There was, therefore, a pure picture of the pathological physiology of the bladder when its parasympathetic supply is greatly reduced, while its sympathetic supply is intact. To correct this imbalance, it seemed justifiable to divide the sympathetic nerves to the bladder, on the hypothesis that they might, through their inhibitory fibres, "over-brake" the efforts of the detrusor

to expel urine. This was accordingly done. The result of the operation was immediate; after his convalescence the patient was able to empty his bladder completely, and when he was examined again, a year after the operation, his cure was maintained.

The second case also was excellent for physiological purposes. A child aged 8 had suffered, at the age of 3 years, from a form of paralysis which affected his lower extremities and his bladder. The highest affected segment of the spinal cord was therefore the second lumbar. Although the paralysis of the legs disappeared, that of the bladder persisted, and when I saw him he had been catheterized three times a day for five years. It seemed to me that here again an intact sympathetic pathway was acting as too effective a restraint upon the activity of the parasympathetic pathway, and that the imbalance might be corrected by division of the sympathetic nerves of the bladder. Happily this proved to be the case, and since the sympathectomy the child has been able completely to empty his bladder.

(*c*) The effect of intravenous injection of adrenaline provides additional evidence.

All available evidence points to the hypothesis that the sympathetic nerves of the bladder provide inhibitory fibres to its detrusor muscle.

(6) Inhibitory fibres to the internal sphincter.—Although it is possible that a few inhibitory fibres pass with its motor fibres in the sympathetic pathway, there is no doubt that the majority reach the internal sphincter by way of the parasympathetic nerves. The best proof of this contention lies in the apparently normal way in which micturition can be carried out after sympathectomy has been performed on a previously normally innervated bladder. The physiology of the internal sphincter will be considered in more detail in a later section.

(7) Vasoconstrictor fibres to the vesical arteries.—I have already pointed out that a certain degree of vasodilatation of the vesical arteries is to be expected as a result of spinal anæsthesia. This is an advantage because the constriction of the vessels, which occurs when the sympathetic pathway is stimulated, is more easily observed. The temporary increase in vasodilatation which follows section of the sympathetic pathway is of much interest; as will be shown, it provides a clue to the nature and origin of that component of the sympathetic pathway which controls tonus in the walls of the vessels.

The sympathetic pathway contains vasoconstrictor fibres for the vesical blood-vessels.

III.—*The segmental levels of the spinal cord associated with the innervation of the bladder.*—(1) Parasympathetic fibres.—There appears to be some variability in the path of the parasympathetic nerves to the spinal cord. Usually they are connected chiefly with the second and third sacral nerves. The branches from the third sacral nerve seem to be constant; those from the second sacral nerve are less constant, and, indeed, Latarjet and Bonnet [10], who speak with authority on the pelvic autonomic system, have never seen branches arising from this nerve. Not infrequently some parasympathetic fibres arise from the fourth sacral nerve; and in an isolated case examined by Cordier [2] there was such a branch from the first sacral nerve.

The second and third sacral are the most important spinal segments connected with the parasympathetic pathway to the bladder.

(2) Sympathetic fibres.—Knowledge of the levels at which vesical sympathetic fibres enter and leave the spinal cord is far from complete. This is largely the result of the intricacy of the connections of the whole thoracico-abdominal sympathetic system, together with the fact that the physiological method of degenerative section of the various nerves is not applicable to man. There are, however, certain points of departure which may be used in studying this aspect of vesical physiology. (*a*) It is known that the whole efferent thoracicolumbar sympathetic system is connected to the spinal cord between the first thoracic and second lumbar spinal segments, inclusive. (*b*) Afferent splanchnic fibres are not limited to this extent of the spinal cord, but may enter it by the anterior or posterior roots of any segment. Foerster's [4] diagram (fig. 7) shows the routes open to such a fibre. (I am not concerned, in this paper, with the relative merits of the "purely efferent" and the "efferent-and-afferent" conceptions of the sympathetic system.)

(*a*) Efferent fibres.—There is no precise evidence available to indicate the segments of the spinal cord which provide motor and inhibitory fibres for the bladder. So far as the skin of the trunk is concerned, it has been shown by Thomas [19], with the aid of the pilomotor reflex, that its sympathetic fibres are derived from the eighth and ninth thoracic segments. On the other hand, the highest roots of the splanchnic nerves are derived from the fifth thoracic sympathetic ganglia, although this level does not necessarily correspond to the spinal level of the preganglionic fibres concerned. If Thomas's conclusions be accepted, it is unlikely that there is a close relationship between the sympathetic innervation of the dermatomes and that of the viscera; but that two spinal segments supply sympathetic fibres

for eleven dermatomes (second to twelfth thoracic) is at least open to doubt.

An accurate origin of the efferent sympathetic fibres to the bladder cannot be given.

(*b*) Afferent fibres.—Some notion of the central connections of the afferent sympathetic fibres to the bladder can be gathered by correlating various scattered observations. It was observed by Head and Riddoch that in cases of total transverse interruption of the spinal cord below the level of the tenth thoracic segment, the passage of a catheter was perceived at the neck of the bladder, and that the patients knew when the bladder was distended. I have already stated that I have been able to produce sensations of pain referred to the bladder by stimulating the sympathetic pathway, when there was analgesia of the skin as high as the tenth thoracic segment. These two observations are complementary. Foerster stated that the afferent sympathetic fibres of the hypogastric nerves reach the spinal cord through the eleventh and twelfth thoracic, and the first, second and third lumbar spinal roots; in the light of my own experience, they must make central connections as high as the ninth thoracic segment. Pieri [17] has attacked the problem by anæsthetizing the spinal roots in turn, until he secured amelioration of vesical pain; he inclines to the view that the third and fourth lumbar roots transmit the majority of the sensory nerves of the bladder, but adds "mes idées là-dessus ne sont pas encore fixées avec certitude." I have had the privilege of discussing this matter with Professor Pieri (December, 1930): he told me he was still uncertain with regard to this point.

Afferent fibres traversing the sympathetic system reach the spinal cord at least as high as the ninth thoracic segment, and probably as low as the fourth lumbar segment.

(3) Somatic fibres.—(*a*) The somatic motor fibres for the external sphincter of the bladder reach the muscle from the third and fourth sacral segments, through the pudic nerve. (*b*) The exact part played by the sensory fibres of the pudic nerve (third and fourth sacral segments) in the innervation of the posterior urethra is doubtful. I have submitted evidence that the major part of the sensory nerve supply of this part of the urethra is by autonomic fibres, through the hypogastric ganglia. Judging from the area to which pain is referred in lesions of the prostatic urethra, these fibres are most likely to be parasympathetic they would thus enter the cord chiefly by the second and third sacral roots.

Part IV.—The Physiology of the Component Parts of the Bladder.

(B) *The detrusor muscle.*—It has been seen that the "detrusor" muscle receives motor fibres from the parasympathetic system, and inhibitory fibres from the sympathetic system. There is no evidence that contraction of the detrusor can be initiated or continued by the direct action of the will. With regard to the inhibitory fibres the position is not nearly so clear, and it will be necessary, at this point, to examine briefly the nature of inhibition in the urinary bladder of the human being. Broadly speaking there are two ways in which these fibres may function. Either they may carry impulses which "unlock" the tonus of the muscle fibres, so that the bladder may be passively dilated to a greater capacity, or they may act as a brake on the force and completeness of the expulsive efforts of the bladder as a whole. The effect of intravenous injection of adrenaline on the capacity of a normal bladder appears to show that fibres are present which function in the first way. In this instance the plastic tonus of the bladder had come into equilibrium with a constant head of fluid; sympathetic stimulation so reduced the tonus as to permit the entrance of a further quantity of fluid. Moreover, for a certain period the plastic tonus of the bladder remained in equilibrium with this increased amount of fluid, though the "head" of fluid in the reservoir, and therefore the fluid pressure exerted on the walls of the bladder, became notably less. Finally, the desire to void made its appearance rather suddenly, at the end of a slow rise of intracystic pressure, although this pressure was at the time notably lower than that exerted by the "head" of fluid at the beginning of the experiment. It may be deduced that sympathetic activity is sufficient to adapt the length of the muscle fibres to accommodate more fluid, although the fluid is offered to the viscus at the same pressure as or even at a lower pressure than, that of the fluid with which the musculature was originally in equilibrium.

On the other hand, the results of sympathetic neurectomy in the two cases cited, in which inability to empty the bladder resulted from functional impairment of the parasympathetic system, the sympathetic system remaining intact, seem to me almost to force acceptance of the hypothesis that sympathetic influences act as a brake on contractions of the detrusor. Furthermore, they must act as a continuous brake, and not merely as a bar to initiation of the contraction of the muscle. Otherwise, the difficulty would lie merely in beginning the flow, and once started the muscle would be able to empty the bladder.

There is here a mechanism the voluntary putting into action of which might be one available method of checking the usual response to the desire to micturate.

There remains to be explained the method by which the bladder accommodates itself to contain a normal amount of urine, after the operation of sympathetic neurectomy. That there is often a definite period required for this accommodation may be judged from the transient frequency of micturition which may follow the neurectomy. Moreover, normal capacity cannot result from passive over-stretching of desympathectomized muscle fibres, for this would be a process limited only by the non-vital factor of limit of stretch, and the last state of the patients would be worse than the first, whereas they have remained cured. Therefore, there must be assigned to the muscle fibre and to the parasympathetic system the ability to acquaint higher nerve centres with the degree of tension under which they find themselves.

(II) *The ureteric orifices.*—Although stimulation of the sympathetic nerves of the bladder leads to simultaneous contraction of both trigone and ureteric orifices, it must, I think, be admitted that the control of these two structures may be dissociated to a certain extent. The evidence for this hypothesis is based on my observation that after the intravenous administration of adrenaline the orifices may open although the trigone is contracted. This evidence is not unassailable, inasmuch as the subject of the experiment is necessarily suffering from an anatomic deformity; moreover, it may be that the orifices are passively opened by the active flow of urine. To clarify the problem it would be essential to secure a number of observations correlating the occurrence of the waves of contraction and dilatation which normally pass over the filling bladder with the opening and closing of the orifices. At present it is not known whether the trigonal musculature participates in these contractions. If there is a neuro-muscular mechanism which arranges that the ureteric orifices be closed when the bladder is contracting, it must also arrange for the ordered delivery of urine from the renal pelvis to the bladder, and the existence of a sufficiently connected nervous network to undertake this work has been described. In addition, the oblique manner in which the terminal part of the ureters enters the bladder tends to prevent reflux up the ureters at each vesical contraction.

(III) *The internal sphincter.*—It has been shown in the preceding parts of this paper that stimulation of the sympathetic nerves of the bladder gives rise to contraction of the internal sphincter. The ability

of the sphincter to remain closed after sympathetic neurectomy proves that it must also possess an inherent tonus of its own. On the other hand, it is a urological commonplace that in so-called "cord bladder" the internal sphincter is found to be relaxed; in these cases the lesion is situated somewhere in the parasympathetic pathway. We are forced to conclude that maintenance of closure of the internal vesical sphincter depends upon its inherent tonus, which in turn depends upon the integrity of reflex fibres in the parasympathetic pathway; and that its sympathetic supply merely reinforces this closure. With regard to the actual closure of the sphincter, after it has been opened, there are two possibilities. The first is that this is initiated by sympathetic nerves; the second is that closure is due to the cessation of inhibitory influences reaching it along parasympathetic fibres. The fact that in the female incontinence does not follow the operation of sympathetic neurectomy disposes of the first hypothesis; for in this sex the external vesical sphincter has little if any independent control of the urinary bladder. It may be concluded, therefore, that closure of the sphincter is due to its own tonic contraction when inhibitory influences cease to reach it. Since it is possible for a woman to interrupt the flow of urine after sympathetic neurectomy, it follows as a corollary that here is one incontrovertible proof that the will can be exerted through the medium of the autonomic nervous system.

With regard to the mechanism of the opening of the sphincter, there are two existing hypotheses. The first is that its tonus is directly relaxed by inhibitory influences passing over parasympathetic nerves; the second, suggested by Young and Davis [22], is that it is opened mechanically by the pull of extensions of the trigonal musculature, which pass within the grasp of the sphincter to insertions in the posterior urethra. As I have shown, stimulation of the sympathetic pathway leads to contraction of both trigone and internal sphincter; contraction of the trigone has not been observed to open the sphincter. It may be concluded that the opening of the internal sphincter is due to inhibition of its natural tonus; it is obvious that it is possible to accomplish this by the exercise of the will, for example, in voluntary micturition.

In both these respects my observations confirm the original work of Rehfisch [18] on the voluntary control of the internal sphincter.

(IV) *The blood-vessels of the bladder.*—Spinal anæsthesia naturally leads to vaso-dilatation in the structures anæsthetized. It was, therefore, to be expected that the vessels of the bladder would be noticeably

dilated during my operations. It was found that the dilatation became notably more pronounced on division of the sympathetic nerves. At first this was a little surprising. In seeking its explanation, I remembered that it had been shown by Adson [1] that complete vaso-dilatation of the vessels of the extremities could be secured only if all the rami communicantes to the limb were divided, and that interruption of the preganglionic fibres was insufficient. Obviously, then, postganglionic vasomotor fibres were interrupted by division of the presacral nerve. Histologically these pass in the middle root. I am inclined to believe, therefore, that the majority of fibres of the presacral nerve which are derived from the intermesenteric plexuses are vasomotor in nature.

(V) *Sensation in the bladder.*—It has been seen that afferent fibres subserving sensation are present in both the sympathetic and the parasympathetic vesical nerves. As a result of my experience with neurectomy of these nerves, it has been possible to determine with a tolerable degree of certainty the paths pursued by the fibres subserving different types of sensation. Parts of the mucous membrane of the bladder are sensitive to touch as well as to painful stimuli. In addition, like all other hollow viscera, its over-distension and its disordered or spasmodic contraction give rise to painful sensations by stretching or squeezing its intramural nervous network. Now it has been an invariable finding after sympathetic neurectomy that relief is obtained from the pain of spasmodic contraction; on the other hand, the most careful examinations have not detected any diminution in the sensitivity of the mucous membrane to tactile or to painful stimuli. Therefore I incline to the view that fibres subserving the latter types of sensation pursue an exclusive parasympathetic route, whereas fibres subserving the former types travel largely by the sympathetic pathway.

(VI) *Afferent fibres for the micturition reflex.*—I have pointed out that after sympathetic neurectomy micturition is normal, so far as it is possible to determine. It has been held by some that the pudic nerves supply a proportion of reflex fibres, on account of their hypothetical sensory distribution to the posterior urethra. I have shown that it is probable that the sensation of the posterior urethra depends on fibres reaching it along autonomic routes; moreover, it has been shown repeatedly that after the operation of bilateral pudic neurectomy [12, 21], the act of passing urine can be carried out in a normal manner. From a physiological standpoint, therefore, it may be concluded that only the parasympathetic pathway is essential for the act of micturition.

Part V.—The Act of Micturition.

Of late years the settling of many debated neurophysiological matters has clarified discussion of the physiology of the act of micturition. Among these may be mentioned the possibility that the will could be exercised by way of autonomic nerves, and the tendency to regard the posterior urethra or the external sphincter as the "trigger zone" for starting the act. Reluctance to accept the former obscured the true explanation of voluntary micturition. The latter hypothesis, revived by Müller in 1918, was an attempt to dispense with the former by substituting an alternative explanation which would be acceptable to current physiological thought.

It seems to me that the simplest way to regard the act of micturition is as a modified autonomic reflex, which may be set in motion and completed by a stimulus applied at one of two points. These reflex "triggers" are the vesical musculature, for which the adequate stimulus is the degree of distension of the viscus, and the internal vesical sphincter. When the adequate stimulus is applied to the first the opening of the internal sphincter is arranged for automatically; this is the mechanism of micturition on desire to urinate. On the other hand, when the internal sphincter is voluntarily relaxed the detrusor muscle automatically contracts; this is the mechanism of voluntary micturition.

It may be urged, reasonably enough, that the term "reflex" is hardly applicable to a process which may be voluntarily interrupted at any point in the cycle. It is true that, in the male at least, there is a possibility that the interruption may be due to the presentation of an insuperable barrier to the outflow of urine by the voluntary closure of the external vesical sphincter. Personal experiment is sufficient to dispose of this hypothesis; for it will be found that sudden interruption of the urinary stream is not followed by a feeling as if the bladder were trying to overcome an obstruction at its outlet. In other words, as the internal vesical sphincter is closed, there is a simultaneous stopping of the contraction of the detrusor muscle, which at once assumes a plastic tonus commensurate with the vesical content at the time. It is also a matter of surgical experience that the urinary flow can be interrupted with a similar lack of discomfort after the operation of prostatectomy, when, owing to the surgical destruction of the internal sphincter, only the external sphincter is available to check the stream. Either the change in the behaviour of the detrusor muscle is the result of a reflex, whose afferent paths may begin either in the internal sphincter (autonomic segment of arc) or in the external sphincter (somatic segment of arc),

or the neural impulses necessary for interrupting the stream are integrated at a higher level, and flow from this level simultaneously to sphincter and detrusor. Obviously the latter hypothesis is the more attractive; and since it has been shown that the parasympathetic is the only peripheral pathway essential for voluntary interruption of the flow, it may be added as a corollary that the integrating centre is situated in the second, third and possibly the fourth sacral spinal segments. If this view be accepted, the conception of micturition as a pure reflex must be limited to infancy, and the gradual development of adult control must be ascribed to the more and more complete subjugation of an originally primitive spinal function to cerebral influences. It is hardly necessary to add that many analogous processes could be mentioned. Be that as it may, there is still to be explained the presence of an adequate external sphincter in the male; in the female it is generally agreed that this structure is so unimportant that it may be discounted in considering the normal physiology of the organ. I must confess that at present no adequate teleological explanation is available.

The term "reflex," then, may be applied correctly to the act of micturition in infants; and it may also be applied to the process of automatic micturition which may follow interruption of the spinal cord at any level compatible with life. It is a fact of supreme physiological importance that the manner in which the bladder empties itself, after the establishment of automatic micturition, is the same at whatever level the cord is injured [20]. The presence of extraspinal reflex centres of sufficient complexity to complete the act must therefore be conceded. The next step is to ascertain the locality of these centres, and this at once raises the question, at what points on their pathway parasympathetic and sympathetic fibres are interrupted by synapses.

It has been shown that approximately 40 per cent. of the fibres of the presacral nerve are postganglionic, and I have advanced the hypothesis that these are vasomotor fibres whose cell stations are situated in the great visceral ganglia and in the scattered ganglion cells which are found in the plexuses about the aorta, and even in the presacral nerve itself. The remainder of the sympathetic fibres, and the parasympathetic fibres, must be interrupted either in the hypogastric ganglia or in the vesical ganglia on the walls of the viscus. If these fibres follow the general morphological rule for autonomic nerves, the sympathetic fibres would be interrupted in the hypogastric ganglia, with the possible exception of those for the internal vesical sphincter, which, as Gaskell [5] pointed out, tend to have their synapses in or near the structure which

they innervate. On the other hand, the parasympathetic fibres would pass through the hypogastric ganglia, to be interrupted in the vesical ganglionic plexuses. An opportunity for settling these points histologically has not as yet presented itself; but the matter will be investigated if and when a suitable case comes to necropsy.

Note on the Innervation of Certain Male Genital Organs.

In the course of my research upon the innervation of the bladder, various points of interest in the innervation of the male genitalia have been brought to light. It has been shown that stimulation of the sympathetic nerves to the pelvis leads to expulsion of semen from the ejaculatory ducts, as a result of contraction of the musculature of the seminal vesicles, and to expulsion of secretion from the prostatic ducts, as a result of contraction of the unstriped musculature which permeates the gland. It is of great physiological interest that, following sympathetic neurectomy, male patients have found that although they could perform the sexual act, and although they experienced a psychical orgasm indistinguishable from the normal, ejaculation did not occur. Now it is known that after the operation of lumbar sympathectomy, in which the second, third, and fourth lumbar ganglia, together with the intervening trunks, are removed, there is no such alteration of sexual function. By a process of exclusion, it is obvious that the motor fibres for the vesicles and efferent ducts must reach the presacral nerve either in the branches which it receives from the first lumbar ganglia or in its middle root. I have presented evidence which makes it probable that the middle root has a vasomotor distribution; it would appear, therefore, that the motor fibres in question pass in the branches from the first lumbar ganglia to the lateral roots of the presacral nerve. It may also be concluded that the sensations constituting the orgasm are not directly associated with contractions of the musculature of the seminal vesicles and ejaculatory ducts.

BIBLIOGRAPHY.

[1] Adson, A. W. Personal communication to the author.

[2] Cordier, Pierre. "Sur l'innervation de l'utérus," *Compt. rend. Soc. de Biol.*, 1921, **84**, 898-900.

[3] Elliott, T. R. "The Innervation of the Bladder and Urethra," *Journ. Physiol.*, 1907, **35**, 367-445.

[4] Foerster, O. "Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände." Berlin: Urban and Schwarzenberg, 1927, 360 pp.

[5] Gaskell, W. H. "The Involuntary Nervous System." New York: Longmans, Green and Co., 1920, 178 pp.

[6] Gil-Vernet, S., and Gallart-Monés, F. "Nouvelle communication nerveuse entre les organes des appareils digestif et génito-urinaires," *Arch. d. Mal. de l'App. digestif.*, 1921, **11**, 105-121.

[7] Head, Henry. "On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease," *Brain*, 1893, **16**, 1-132.

[8] Head, Henry, and Riddoch, George. "The Automatic Bladder, Excessive Sweating and some other Reflex Conditions, in Gross Injuries of the Spinal Cord," *ibid.*, 1917, **40**, 188-263.

[9] Hovelacque, A. "Anatomie des nerfs craniens et rachidiens et du système grand sympathique chez l'homme." Paris: Gaston Doin et Cie, 1926, 880 pp.

[10] Latarjet, A., and Bonnet, Paul. "Le plexus hypogastrique chez l'homme," *Lyon Chir.*, 1913, **9**, 619-644.

[11] Laux, G. "Contribution a l'étude anatomique du sympathique pelvien. Deductions chirurgicales." Lyon: Bosc Frères et Riou, 1928, 200 pp.

[12] Learmonth, J. R. "Leucoplakia vulvitis," *Proc. Staff Meetings, Mayo Clinic*, 1931, **6**, 7-8.

[13] Learmonth, J. R., and Braasch, W. F. "Resection of the Presacral Nerve in the Treatment of Cord Bladder," *Surg., Gynec., and Obst.*, 1930, **51**, 494-499.

[14] Moore, T. D. "Bladder Sensibility," *Arch. Surg.*, 1924, **9**, 176-187.

[15] Müller, L. R. "Die Blaseninnervation," *Deutsch. Arch. f. klin. Med.*, 1918, **128**, 81-106.

[16] Petit-Dutaillis and Flandrin. "Anatomie chirurgicale des nerfs du rein," *Bull. et Mém. Soc. Anat. de Paris*, 1923, **93**, 635-647.

[17] Pieri, Gino. "Énervation ou ramisection?" *Presse Méd.*, 1926, **72**, 1141-1142.

[18] Rehfisch, Eugen. "Ueber den Mechanismus des Harnblasenverschlusses und der Harnentleerung," *Virchow's Arch. f. Path. Anat. u. Physiol.*, 1897, **150**, 111-151.

[19] Thomas, André. "Le réflexe pilo-moteur." Paris: Masson et Cie, 1921, 252 pp.

[20] Thomson Walker, J. W. "The Bladder in Gunshot and other Injuries of the Spinal Cord," *Lancet*, 1917, **1**, 173-179.

[21] Wertheimer, P., and Michon, L. "La névrotomie du nerf honteux interne: indications, technique, résultats," *Journ. de Chir.*, 1928, **31**, 497-509.

[22] Young, H. H., and Davis, D.M. "The Practice of Urology." Philadelphia: W. B. Saunders Company, 1926, 1484 pp.

[23] Young, H. H., and Macht, D. I. "A Contribution to the Physiology and Pharmacology of the Trigonum Vesicæ," *Journ. Pharmacol. and Exper. Therap.*, 1923, **22**, 329-354.

THE COMPONENT REFLEXES OF MICTURITION IN THE CAT.

Parts I and II.

BY F. J. F. BARRINGTON.

(From the Laboratories of the Surgical Unit, University College Hospital Medical School.)

Five component reflexes of micturition in the cat have been described [Guyon, 1900], [Barrington, 1914], namely:—

(1) A hind-brain reflex evoked by distending the bladder, effecting a contraction of the bladder and having both its afferent and efferent paths in the pelvic nerves.

(2) A hind-brain reflex evoked by running water through the urethra, effecting a contraction of the bladder and having its afferent path in the pudic and its efferent in the pelvic nerves.

(3) A spinal reflex evoked by distending the proximal urethra, effecting a slight, transitory contraction of the bladder and having both its afferent and efferent paths in the hypogastric nerves.

(4) A spinal reflex evoked by running water through the urethra, effecting relaxation of the urethra and having both its afferent and efferent paths in the pudic nerves.

(5) A spinal reflex evoked by distending the bladder, effecting a relaxation of the urethra and having its afferent path in the pelvic and its efferent in the pudic nerves.

Part I.

If the five reflexes mentioned were the only ones existing, division of the pelvic nerves in a cat, in which the spinal cord, near the level of the last rib, and the pudic nerves had previously been divided, would not produce any increase in the volume of residual urine. The following four experiments show that in fact such an increase does occur. Experiment 4 shows further that this increase is a result of division of nerve fibres and not of some other lesion made at the operation.

(1) Female. Pudic nerves divided, and five to six weeks later the spinal cord transected in the last thoracic and first lumbar segments.

6th day	..	Residual urine	..	115 + (5) c.c.
14th ,,	..	,, ,,	..	120 + (10) c.c.
20th ,,	..	,, ,,	..	90 c.c. or less.
25th ,,	..	,, ,,	..	60 c.c. or less.
29th ,,	..	,, ,,	..	70 c.c.
33rd ,,	..	,, ,,	..	65 c.c.
41st ,,	..	,, ,,	..	80 c.c. Pelvic nerves divided.
45th ,,	..	,, ,,	..	170 c.c. (Hæmaturia.)
49th ,,	..	,, ,,	..	250 c.c.
54th ,,	..	,, ,,	..	285 c.c. (Cystitis.)

(2) Castrated male. Pudic nerves divided and spinal cord transected in the last thoracic and first lumbar segments.

4th day	..	Residual urine	..	135 + (40) c.c.
9th ,,	..	,, ,,	..	185 c.c.
17th ,,	..	,, ,,	..	45 c.c.
25th ,,	..	,, ,,	..	120 c.c.
30th ,,	..	,, ,,	..	50 c.c.
37th ,,	..	,, ,,	..	90 c.c.
40th ,,	..	,, ,,	..	75 c.c. or less. Pelvic nerves divided.
46th ,,	..	,, ,,	..	195 c.c.
51st ,,	..	,, ,,	..	205 c.c.
54th ,,	..	,, ,,	..	175 c.c. + (25) c.c.

(3) Female. Pudic nerves divided and spinal cord transected in the last thoracic segment.

3rd day	..	Residual urine	..	110 c.c. + (an unknown volume) or less.
8th ,,	..	,, ,,	..	100 c.c. + (10) c.c. or less.
11th ,,	..	,, ,,	..	215 c.c. + (10) c.c.
13th ,,	..	,, ,,	..	125 c.c. + (50) c.c.
17th ,,	..	,, ,,	..	120 c.c. + (10) c.c.
19th ,,	..	,, ,,	..	125 c.c.
21st ,,	..	,, ,,	..	140 c.c. or less.
25th ,,	..	,, ,,	..	80 c.c.
29th ,,	..	,, ,,	..	110 c.c.
32nd ,,	..	,, ,,	..	170 c.c. Pelvic nerves divided.
37th ,,	..	,, ,,	..	225 c.c.
42nd ,,	..	,, ,,	..	220 c.c.
47th ,,	..	,, ,,	..	175 c.c.
51st ,,	..	,, ,,	..	115 c.c. (Hæmaturia).
56th ,,	..	,, ,,	..	125 c.c. or less (Hæmaturia).
59th ,,	..	,, ,,	..	160 c.c. (Hæmaturia).
63rd ,,	..	,, ,,	..	85 c.c.
67th ,,	..	,, ,,	..	85 c.c. + (20) c.c. or less.
71st ,,	..	,, ,,	..	130 c.c.
78th ,,	..	,, ,,	..	55 c.c.
80th ,,	..	,, ,,	..	40 c.c.
88th ,,	..	,, ,,	..	85 c.c.
94th ,,	..	,, ,,	..	35 c.c.
99th ,,	..	,, ,,	..	110 c.c.
101st ,,	..	,, ,,	..	85 c.c.

(4) Female. Inferior mesenteric ganglia excised and spinal cord transected in the last thoracic segment. Fifty-one days later the pudic nerves were divided.

6th day	..	Residual urine	..	12 c.c.
9th ,,	..	,, ,,	..	15 c.c.
10th ,,	..	,, ,,	..	10 c.c.
12th ,,	..	,, ,,	..	7 c.c. sacral spinal roots divided.
14th ,,	..	,, ,,	..	50 c.c.
16th ,,	..	,, ,,	..	85 c.c.
18th ,,	..	,, ,,	..	130 c.c.
24th ,,	..	,, ,,	..	155 c.c.
31st ,,	..	,, ,,	..	75 c.c.
37th ,,	..	,, ,,	..	45 c.c.

In the above descriptions, when a residual urine is stated to be a certain volume "or less," it means that such a volume was obtained by emptying the bladder by expression, but that it was not known that the last previous passage of urine was so short a time before that the volume secreted in the interval was negligible. When a second figure in brackets is given after a + it means that the first volume was measured and that some urine was still left in the bladder the volume of which was estimated, from the size the bladder felt, to be that in the brackets.

Therefore, there must exist a spinal reflex, or reflexes, having both paths in the pelvic nerves and effecting a relaxation of the urethra, or a contraction of the bladder, or both. In the four experiments just described it was not obvious from the feel of the bladder, when it was being expressed, that the resistance of the urethra was increased after division of the pelvic nerves.

An attempt to obtain direct evidence of such reflex relaxation of the urethra was made in the following way. Female cats only were used. The cat was anæsthetized with chloroform, a spinal transection made about the level of the last rib and both pudic and both hypogastric nerves were divided. The pelvic nerves were then freed and a thread put loosely round each. The cat was then decerebrated, the administration of chloroform stopped, and at least half an hour allowed to elapse before going on with the experiment. A brass catheter was then passed and the bladder emptied. The catheters used were numbers 5 and 7 (Charrière), i.e., $\frac{5}{3}$ and $\frac{7}{3}$ millimetres in diameter; size 5 appeared the better. The catheter was then connected with a graduated, warm water reservoir fitted with a clamp and capable of being raised and lowered to given heights, to alter the pressure of the water at the catheter when the clamp was open. A given height of the water above the catheter being kept constant, the water was allowed to run in the catheter until the volume run in did not increase. The height was then increased a known amount and the same process repeated until water was seen to escape from the urethra alongside the catheter, and the pressures when this just did not and just did occur were noted. In this way no clear results were obtained because there was a continual rise in the bladder volume for each given intravesical pressure and a continual rise in the intravesical pressure necessary to cause escape of water from the urethra, as successive observations were made, before division of the pelvic nerves.

A second set of experiments were made in the same way except that the transection was made, with or without the division of the pudic or hypogastric nerves or of both, and an interval of two weeks or more

allowed to elapse before isolating the pelvic nerves, dividing the pairs of nerves remaining, and decerebrating the cat. The experiments were then proceeded with as before. In them, as in other experiments where an interval was allowed to elapse between the nerve division and the final operation, the inferior mesenteric ganglia were excised at the time of division of the hypogastric nerves and 1 to 2 cm. of the pudic nerve excised at the time of its division. The results are shown in the following table.

Interval, in days, between the spinal transection and the decerebration	Nerves divided at the time of the transection	Minimum intravesical pressure, in centimetres of water, which lead to the escape of water from the urethra	
		Before division of the pelvic nerves	After division of the pelvic nerves
14	Hypogastrics	(1) 7½ to 10 (2) Less than 7½ (3) 5 to 6 (4) Less than 6 (5) ,, ,, 7½ (6) ,, ,, 7½	(7) 15 to 17½ (8) 12½ to 15
23	Hypogastrics	(1) Less than 7½ (2) 7½ to 10 (3) Less than 12½ (4) ,, ,, 12½ (5) ,, ,, 12½	(6) 16½ to 17½ (7) More than 15 (8) ,, ,, 15
25	Hypogastrics	(1) Less than 10 (2) 7½ to 10	(3) 20 to 22½
31	Hypogastrics	(1) 7½ to 10 (2) 7½ to 10 (3) 13 to 14	(4) 15 to 20 (5) 15 to 17½ (6) 25 to 30
35	None	(1) 10 to 20 (2) Less than 12 (3) 15 to 20 (4) 12½ to 15 (5) 12½ to 15	(6) Less than 15
38	None	(1) 20 to 25 (2) Less than 10 (3) 5 to 7½ (4) Less than 7½ (5) ,, ,, 7½	(6) 10 to 15 (7) 10 to 12½
66	Hypogastrics and pudics	(1) 10 to 15 (2) Less than 10 (3) ,, ,, 10	(4) 17½ to 20 (5) 17½ to 20

Therefore in six out of the seven experiments there is a well-marked increase in the intravesical pressure necessary to force open the urethra after division of the pelvic nerves. In the remaining experi-

ment, the fifth, there is no such increase, this cat had an infective cystitis and it was the only one of the seven which had.

Three other experiments were made in a slightly different way. The spinal cord was transected in the last thoracic or first or second lumbar segments and the inferior mesenteric ganglia excised under chloroform and ether. After an interval of three weeks or more chloroform was given, the pudic nerves divided, the pelvic nerves exposed and a cannula tied into the fundus of the bladder at the attachment of the urachus. The cat was then decerebrated and the chloroform stopped. After an interval the bladder was emptied through the cannula and the latter connected with the same graduated warm water reservoir used in the previous series of experiments. By raising and lowering the reservoir the minimum pressure which gave rise to the escape of water from the external urinary meatus was found. The results are shown in the table.

Interval, in days, between the spinal transection and the decerebration	Nerves divided at the time of the transection	Minimum intravesical pressure, in centimetres of water, which lead to the escape of water from the urethra	
		Before division of the pelvic nerves	After division of the pelvic nerves
21	Hypogastrics	(1) 4 to 5 (2) 4 to 5	(3) 11 to 12 (4) 9 to 10
22	Hypogastrics	(1) 5 to 6 (2) 3 to 4 (3) 4 to 5 (4) 4 to 5	(5) 10 to 11 (6) 8 to 9 (7) 8 to 9
24	Hypogastrics	(1) 8 to 9 (2) 7 to 8	(3) 8 to 9 (4) 5 to 6

In the first and second experiments a well-marked increase in the intravesical pressure necessary to cause the escape of water from urethra followed division of the pelvic nerves. The third cat differed from the first two in having an infective cystitis: this had been present eight days. The cystitis was slight, œdema of the subepithelial tissue was present but no ulceration and the general health of the cat was unaffected: other reflexes from the bladder, such as the production of perineal contractions, were obtained in this cat.

In the ten experiments contained in these two series, therefore, there was an increase in the urethral resistance following division of the pelvic nerves except in the only two in which cystitis was present. It follows from this that there is a spinal reflex, having both paths in the

pelvic nerves, evoked by distension of the bladder and effecting relaxation of the urethra.

A third set of experiments was done in the same way as the last two, except that instead of passing a catheter or of tying a cannula into the fundus of the bladder, the bladder neck was divided, a cannula tied into each cut end, and the cannulæ connected with vessels of warm water whose pressures could be altered at will by altering the water levels [Barrington 1921]. In these experiments no diminution of the urethral resistance could be found as the result of increasing the intravesical pressure. As the table shows, no increase in the minimal urethral resistance leading to the escape of water from the external meatus followed division of the pelvic nerves. It appears from the table that the urethral resistance left after the division of the pudic nerves increases in the course of thirteen to seventeen days, but this fact does not concern the present question.

The cannula tied into the distal end of the divided neck of the bladder in these experiments measured 7 mm. from its neck to its tip

Interval, in days, between the spinal transection and the decerebration	Nerves divided at the time of the transection	Minimum pressure in centimetres of water, which lead to the escape of water from the urethra: Before division of the pelvic nerves	After division of the pelvic nerves
13	Hypogastrics and pudics	(1) 20 to 25 (2) 20 to 25	(3) 20 to 25
14	Hypogastrics and pudics	(1) 25 to 30 (2) 20 to 25 (3) 20 to 25	(4) 20 to 25
17	Hypogastrics and pudics	(1) 25 to 30 (2) 25 to 30 (3) 25 to 30 (4) 30 to 35	(5) 5 to 15
17	Hypogastrics and pudics	(1) 20 to 30 (2) 30 to 35 (3) 25 to 30 (4) 20 to 25	(5) 15 to 20
15	Hypogastrics	(1) 7½ to 10 (2) 5 to 7½ (3) 5 to 7½	(4) 5 to 7½
15	Hypogastrics	(1) 15 to 20 (2) 10 to 15 (3) 10 to 15 (4) 10 to 15	(5) 12½ to 15 (6) 12½ to 15
16	Hypogastrics	(1) 10 to 15 (2) 5 to 10	(3) 5 to 10

and $2\frac{1}{2}$ mm. in diameter at its tip. Allowing for the part of the urethra between the ligature and the section and for the part held open by the end of the cannula, at least $1\frac{1}{4}$ cm., or approximately one-third, of the urethra is mechanically thrown out of action at its proximal end. In order to determine whether the increase in urethral resistance following division of the pelvic nerves was absent in these experiments because of the functional absence of the proximal third of the urethra, or because of the dissection of the bladder neck which was made in them, but not in the previous experiments, five further experiments were made. These were made in exactly the same way as those of the second series described, by using a single cannula tied into the fundus of the bladder, with the single addition that the neck of the bladder was exposed just before the decerebration and a hook put round it and withdrawn. The results of these five experiments were that an increase in the urethral resistance followed the division of the pelvic nerves in three experiments, a diminution in one and no alteration in the fourth. Cystitis was not present in any of the four. It therefore seems that the preliminary dissection of the neck of the bladder must interfere with the usual result of dividing the pelvic nerves in a considerable proportion of cases, but not in such a proportion as to completely abolish it in seven successive experiments. The part of the urethra chiefly concerned in the increased resistance is therefore the proximal third.

It is concluded that a sixth reflex exists, which is spinal. It is evoked by distending the bladder and effects a relaxation of the plain muscles of the urethra, chiefly or entirely in its proximal third. Both its paths are in the pelvic nerves.

In the second series of experiments, that in which the single cannula was tied into the bladder fundus, it was seen that individual intravesical pressures, lower than that which caused the escape of water from the urethra, were not associated with a significant increase in the corresponding bladder volumes after division of the pelvic nerves. This does not show that there is no spinal reflex contraction of the bladder evoked by distension, but it does show that if such exists it cannot be a factor in the increase of the residual urine resulting from division of the pelvic nerves, described at the beginning of this paper, until the abolition of the sixth reflex has given it a chance of showing itself.

REFERENCES.—PART I.

Barrington, F. J. F. (1914), *Quart. J. Exp. Physiol.*, **8**, 33.
Barrington, F. J. F. (1921), *Brain*, **44**, 23.
Guyon, J. F. (1900), *C.R. Soc. Biol. Paris*, 712.

Part II.

If the spinal cord is divided in posterior thoracic or anterior lumbar region and the bladder emptied at the time of the operation, urine is not usually passed for three or four days. The cat then becomes soaked with urine, and contractions of the perineum occur at irregular intervals. Urine comes away very frequently in very small amounts, usually in association with perineal contractions. The residual urine increases for a day or two after the urine has first started to overflow. This first stage of retention with overflow is associated with hæmaturia in a considerable proportion of experiments. Perineal contractions may be evoked by squeezing the distended bladder before urine has begun to overflow. After the latter has occurred, squeezing the bladder leads to an increase in the frequency of the perineal contractions, and, with a longer time or more pressure, to the escape of urine from the urethra in a series of jets having the same periodicity as the perineal contractions. The resistance of the urethra can be felt to be very strong and to be stronger in males than in females, it can be felt to diminish during the time each jet is escaping. It is not possible, at this stage, to empty the bladder with any moderate pressure without a general anæsthetic, since when the bladder has become less tense from the loss of urine the urethral resistance can be felt to have increased. As far as can be felt, the urethral resistance can be made to vanish, without any preliminary diminution, if chloroform is given; the bladder can then be emptied by squeezing it with quite low pressure. The abolition of the palpable urethral resistance with chloroform does not occur until about the time at which respiration stops, more often a few seconds after than a few seconds before, and when it occurs a few seconds before, respiration generally ceases even though the administration was stopped directly the urethral resistance vanished. The urethral resistance, having been abolished with chloroform, remains absent for at least a minute after spontaneous respiration has become re-established. The palpable urethral resistance of an intact cat behaves in the same way under the influence of chloroform.

At the end of the first week the condition is markedly altered, whether the overflow has been allowed to continue all the time, or whether the cat has been once chloroformed and the bladder completely emptied, in which case it will have begun to overflow for the second time. The residual urine and the palpable urethral resistance are now both diminished, and, in consequence of the latter, it is generally easy to empty the bladder without giving chloroform.

By the end of the second week there is a still further reduction in the volume of residual urine, and in a palpable urethral resistance. The urethral resistance is now commonly only just palpable, but its existence is quite obvious from the fact that when the bladder is squeezed the urine escapes in jets, as it did in the first stage. From this period onwards the urethral resistance remains the same, as far as can be felt, but the residual urine often increases in volume in the fourth or fifth weeks, but it never again reaches that which it was at the beginning of the overflow.

The cat has now arrived at the so-called automatic micturition stage, which is permanent unless modified by the supervention of some pathological condition. It is evident that the lowered urethral resistance is an important, and possible that it is the only, factor in the transition from the stage of retention with overflow to that of automatic micturition. It is the purpose of the present paper to inquire into what the lowered urethral resistance is due.

The urethral resistance, felt so readily in the stage of retention with overflow, and, less easily, in the stage of automatic micturition, must be due to the contraction of the compressor urethræ, since, after a spinal transection the urethra proximal to the compressor urethræ is full of urine at other times than when urine is being passed (Barrington, 1914). This being so, the resistance must be maintained through efferent fibres in the pudic nerve. If both pudic nerves are divided at the same time as, or previous to, the spinal transection, it is found that the overflow of urine occurs sooner, and, as soon as it has occurred, the urethral resistance which can be felt on squeezing the bladder is very low or absent. The observations of Masius (1868) on rabbits and dogs pointed to the same conclusion. He showed that the urethral resistance following spinal transections in front of certain levels was abolished if the cord behind such a transection was destroyed.

Many experiments were made by excising the inferior mesenteric ganglia at the same time as the spinal transection was made. The results did not differ qualitatively from those of the transection alone. It did appear that the diminution in the urethral resistance and in the volume of residual urine occurred rather more quickly, that the final volume of residual urine in most cases was rather less, and that hæmaturia in the retention and overflow stage was less frequent; in any case these quantitative differences were small, and it is possible that enough experiments were not done to establish their existence at all.

It has been shown previously (Barrington, 1914), that a firm, persistent contraction of the compressor urethræ occurs after division of the dorsal sacral roots on both sides and that this remains unaffected by subsequent division of the hypogastric nerves. The contraction of the compressor urethræ is maintained, therefore, after division of the afferent fibres in the pudic nerve but not after division of the efferent fibres.

The diminution of the contraction of the compressor urethræ following a spinal transection might be due to weakening of the muscle or to an increase in the effect of one or more of the reflexes which normally relax it. If the former supposition be true, division of both pelvic nerves would appear unlikely to prevent the diminution in urethral resistance following a spinal transection and could not possibly restore the urethral resistance after the diminution had taken place. On the other hand, if the fifth reflex, mentioned at the beginning of this paper, is acting more effectively, division of both pelvic nerves at the time of the transection should prevent the diminution in urethral resistance occurring, and division after the diminution has taken place should restore the resistance to its original strength.

Spinal transection subsequent to, or at the same time as, division of both pelvic nerves was found to be a very fatal operation by reason of the effect on the bladder. Only two cats so operated on survived more than a week, which is the least period from which any conclusion can be drawn. In one of these the urethral resistance remained very great up till the thirteenth day, had diminished but was still considerable on the fifteenth and was nearly absent on the sixteenth when cystitis was obvious and the cat was killed. In the second the resistance remained very great until the tenth day when the cat was accidentally killed with chloroform which was being given for the purpose of emptying the bladder. In both cats, therefore, the urethral resistance remained strong far longer than would have been the case if the pelvic nerves had been intact.

Hæmaturia is not uncommon after simple spinal transections but, at least in female cats, is seldom serious and only very rarely fatal. The bladder, when the condition is present, shows numerous small ecchymoses which are just beneath the epithelium. The epithelium over them is shed in places. The condition, therefore, arises from rupture of vessels forming the plexus immediately deep to the epithelium: these vessels are all small. When the transection is combined with division of the pelvic nerves hæmaturia is much more frequent

and quite commonly fatal. In the fatal cases the animals show no local symptoms but become listless and drowsy and die in a few hours. The bladder in such cases is purple in colour and its walls are lax and infiltrated with blood throughout. The bladder contents may contain organisms in animals that have died. If the cat is killed as soon as it shows signs of illness, though the changes in the bladder wall are well-advanced, no organisms can be found in its contents, obtained aseptically, either in films or by culture on agar: the condition is, therefore, primarily mechanical and not primarily infective. Sections of the bladder at this stage show that the epithelium is largely shed and that small vessels immediately deep to it are greatly distended with blood, a large amount of extravasated blood is present between the muscular fasciculi and in the areolar tissue on their internal surface and that in places the muscle fibres are fragmented and stain badly, their nuclei having become cork-screw-shaped and in places granular. These appearances show that the condition is due to rupture of the large vessels which are situated in the areolar tissue close to the internal side of the muscle leading to necrosis of the bladder. The only mechanical condition present capable of producing this change is distension of the bladder. This, therefore, must be greater or more prolonged after the pelvic nerves have been divided with the transection than after the transection by itself.

In three cats, which had had a transection in the last thoracic or first lumbar segment, the pelvic nerves were divided after an interval of fourteen to forty-five days. In all there was a great increase in the urethral resistance easily palpable on squeezing the bladder, and this remained high until the animals were killed on the fourth to the twelfth days after division of the nerves. The increase of urethral resistance following division of the pelvic nerves was measured in three cats which had had transection in the first lumbar segment and excision of the inferior mesenteric ganglia twelve to sixteen days previously. The cats were decerebrated. In two a cannula was tied into the bladder fundus and connected with a warm water reservoir which could be raised and lowered and the lowest pressure which led to the escape of water before and after the division of the pelvic nerves noted. Division of the pelvic nerves was followed in one by a rise of urethral resistance from 5 to 6 cm. of water to 23 to 24 cm. of water, and in the other by a rise from 7 to 8 cm. to 30 to 31 cm. In the third cat the bladder neck was divided and cannulæ tied into each cut end. The water pressure necessary to force the urethra was measured before and after division of

the pelvic nerves with the bladder pressure at 10 cm. of water. It was 15 to 17½ cm. before and 25 to 30 cm. after division of the nerves.

Division of the pelvic nerves, therefore, at the time of a spinal transection prevents the diminution in the urethral resistance, which would otherwise follow the transection, from occurring, and division of these nerves after the diminution of the resistance has taken place restores it. It is therefore concluded that the diminution in the urethral resistance following the transection results from an increased effectiveness of the fifth reflex mentioned at the beginning.

REFERENCES.—PART II.

BARRINGTON (1914), *Quart. J. Exp. Physiol.*, **8**, 33.

MASIUS (1868), *Bull. de l'Acad. royale des Sciences, des Lettres et des Beaux-arts*, 2me serie, **25**, 491.

KORSAKOFF'S SYNDROME: ITS HISTOPATHOLOGY.

BY E. ARNOLD CARMICHAEL AND RUBY O. STERN.

(From the National Hospital, Queen Square, London, and Medical Professorial Unit, St. Bartholomew's Hospital.)

INTRODUCTION.

MUCH confusion still appears to exist regarding the clinical and pathological entity of the syndrome which Korsakoff described in 1887, and to which Jolly, at the Moscow Medical Congress of 1897, gave the name "Korsakoff's disease." This designation is untenable in the modern sense of the term "disease," for Korsakoff himself described the syndrome as occurring during the course of many different clinical conditions. As Korsakoff's original paper in Russian is unobtainable in this country it is difficult to be certain of his exact description of the syndrome, for in his later contributions to German journals [13], [14], he refers constantly to his original paper without precisely indicating its contents. But from his articles, and from those of Serbski [28], his co-worker, it is clear enough that what Korsakoff observed and described was a peculiar psychical state characterized by amnesia, disorientation in time and space and a tendency to fabrication, associated with the symptoms and signs of a peripheral neuritis. To-day the terms "Korsakoff's syndrome" or "Korsakoff's psychosis" are used indiscriminately, especially by psychologists, to denote any condition in which a psychical disturbance of this particular type occurs; the physical side of the syndrome may be ignored, or receive scant attention. If we are to use the term "Korsakoff's syndrome" at all, it should be restricted to the condition which Korsakoff observed and not applied only to the psychical state which occurs in that condition.

We began this study of a series of cases of Korsakoff's syndrome in order to determine whether any constant histopathological changes in the brain which might account for the peculiar psychical disturbances could be revealed by modern staining methods. We were at once faced by the difficulty of deciding which cases in the literature could properly be included under the syndrome. It became necessary, in order to limit our review of the pathological findings which have been described in psychical states resembling those found in the true Korsakoff syndrome,

to ignore those cases in which there were no definite clinical signs of a peripheral neuritis or in which the diagnosis of peripheral neuritis was not confirmed by subsequent pathological investigation.

The conception that Korsakoff's syndrome is associated particularly with the peripheral neuritis caused by alcohol poisoning is fostered by the fact that this is perhaps the most common of all forms of neuritis. Although in the five cases of Korsakoff's syndrome we have to record the cause of the peripheral neuritis was alcoholism, an analysis of the literature revealed many causative factors other than alcohol, and we regret that we have not had the opportunity to include in our series cases in which another factor than alcohol was present.

Ætiology.

It is pertinent to discuss shortly the ætiology of Korsakoff's syndrome before attempting to discuss the lesions which have been recorded pathologically, because the earliest pathological investigation which Korsakoff [13] carried out was on a case which developed after an extra-uterine pregnancy. Only later did he examine the nervous system of alcoholics who succumbed. From Korsakoff's own work and from the work of many subsequent observers, there can be little doubt that a toxæmia is the essential factor in the production of the syndrome, the nature of the toxin depending on the disease from which the patient suffers or on the poison which has been absorbed. Amongst many cases which Korsakoff reported clinically in which an endogenous toxin produced the typical syndrome, he mentioned puerperal fever, septicæmia, typhoid, typhus, diabetes, jaundice, lymphadenoma, tuberculosis, and certain cases of tumour, of which Serbski also gave an example in the case of a woman in whom the syndrome developed immediately after an operation for the removal of an ovarian dermoid.

Korsakoff [14] pointed out, however, that although the nervous system appeared to be particularly susceptible to the effects of alcohol, in that a large proportion of cases occurred in alcoholics, it might well be that the effect of the alcohol was to render the nervous tissue more liable to damage by other toxins, and that alcohol itself was not essentially the toxin responsible.

The recent work of Marcus [18], [19], [20], appears to confirm Korsakoff's view. Marcus reported twelve cases, in three of which the alcoholic factor could definitely be excluded, these being cases of beri-beri, influenza and encephalitis lethargica. But in all the alcoholic cases other disease processes were also operative, which included syphilis,

pneumonia with nephritis, diabetes, acute pleurisy, acute nephritis, polyarthritis with jaundice, hepatic disease (probably cirrhosis). From this series of cases Marcus concluded that another factor besides alcohol was necessary for the production of the syndrome, and that this factor may sometimes give rise to the syndrome in the absence of alcoholism.

The evidence that the syndrome is primarily due to a toxæmia rests upon the fact that although it has been observed in severe forms of nearly every known disease (Mourreye [25], described a case which occurred during a severe attack of scarlet fever), it occurs most frequently in the common conditions in which a toxic factor is supposedly present, such as alcoholism and the toxæmias of pregnancy, especially hyperemesis gravidarum. Before Korsakoff described the syndrome it had been known for some years, as Ely [5] rightly maintained, that psychical disturbances accompanied by peripheral neuritis might occur in women who suffered from excessive vomiting during pregnancy, but the syndrome had not been described as a clinical entity until Korsakoff published his paper. Since then the subject of the occurrence of the syndrome in pregnant women has been fully dealt with by Von Hösslin [11], in his paper on the nervous complications of pregnancy, and a large number of cases has been recorded by various observers, notably by Ledoux [17], Ely [5], Weill-Hall et Layain [32], Dupouy et Courtois [4]. In all these cases the syndrome followed pernicious vomiting and nearly all the patients recovered after the pregnancy had been terminated either by delivery or by therapautic abortion. When death ensued, exhaustion rather than the neurological symptoms was accepted as the cause.

Much attention has been focused during the last decade on the subject of subarachnoid hæmorrhage, and Goldflam [7] was the first to draw attention to the fact that Korsakoff's syndrome is a common sequel to this vascular accident. The syndrome does not develop immediately after the hæmorrhage, but about three weeks later. Hall [10] described two cases of subarachnoid hæmorrhage in both of which the syndrome developed three weeks after the hæmorrhage. This late onset of the syndrome lends support to the essential presence of a toxic factor in the production of the syndrome, since presumably it is the absorption of disintegration products of the shed blood which gives rise to the syndrome. Goldflam maintains that as the prognosis in cases of subarachnoid hæmorrhage which develop a Korsakoff syndrome is good the changes in the brain must be of a recoverable nature.

Speculation on the nature of the toxic factor in other conditions in which Korsakoff's syndrome occurs would be valueless. But in the alcoholic cases it is probable that, as Marcus [18] suggests, another factor is always operative. Alcohol is not a cumulative poison and excretion is very rapid. Yet in most of the alcoholic cases there is a history of continuous steady drinking for many years until the syndrome develops and then in the fatal cases the course of the disease is short. If defective excretion of the alcohol were responsible for the rapid course of the symptoms, the condition might reasonably be expected to resemble that of acute alcoholic poisoning. There is no similarity however. Nor is there any resemblance to simple chronic alcoholism. It is reasonable to suggest that the imbibition of alcohol in sufficient quantities over a prolonged period lowers tissue resistance and permits degeneration of the nervous system to take place through the action of toxins, or through lack of essential nutritive factors.

Pathological Literature.

The majority of pathological investigations which have been made have been on alcoholic cases and we propose to confine our review of the pathological findings to these cases, but we include the first pathological record of a case presenting the syndrome because Korsakoff [15] himself described it.

The case was that of a woman who developed the syndrome following an operation for an ectopic gestation. She died two months later, remaining in the same psychical state until death, whilst the neuritis was slowly progressive. Microscopically the brain showed no changes whatsoever. (The only stains were those of Weigert and carmine.) There was an increase of the connective tissue of the column of Goll in the spinal cord and a widening, either congenital or due to artefact, of the central canal. The third, fifth, sixth, eighth and tenth cranial nerves showed Wallerian degeneration with Marchi's method, that in the vagus being the most severe. There was a simple parenchymatous degeneration in the peripheral nerves, more advanced distally than proximally. The muscles had undergone a simple atrophy.

In an alcoholic case, of which only a short summary is given, Korsakoff and Serbski [15] found a thickening of the cortical vessels and an increase in the connective tissue (? neuroglia) of the cerebral cortex.

Ballet et Faure [1] reported two cases with post-mortems. In both there was fatty degeneration of the liver and in one a slight cirrhosis.

The pyramidal cells in the motor cortex were chromatolytic. No other changes were found in the brain. In one case the anterior horn cells in the lumbar region of the spinal cord were also chromatolytic; in the other they appeared normal. No degeneration of the posterior columns of the spinal cord was found in either case. In both cases there was degeneration of the peripheral nerves.

A. Meyer [23] in discussing "axonal reaction" described the Betz cells which he observed in the motor cortex of a patient who had exhibited Korsakoff's syndrome during life as examples of this reaction. He found similar chromatolysis in the cells of the frontal region, and in all the nuclei of the medulla, except the hypoglossal. A few degenerating fibres were seen in the crus, in the splenium of the corpus callosum and in the thalamus, but these did not correspond to the great degeneration of the pyramidal cells in the cortex. Meyer did not regard this finding of degenerate pyramidal cells as peculiar to the pathology of the Korsakoff syndrome, as he had found the same degeneration present in most forms of insanity. Turner [30] also found degeneration of the Betz cells in a case in which he examined the brain, but he considered that this was consecutive to the extensive degeneration of the crossed pyramidal tracts which was present in the spinal cord. Turner also found degeneration of the posterior columns of the spinal cord and made the statement, which we have been unable to confirm, that every case presenting the Korsakoff syndrome examined pathologically up to that time had shown degenerative changes in these tracts. The anterior horn cells in the lumbar region were extensively degenerated and a large proportion of the cells of the dorsal root ganglia appeared chromatolytic. Turner [31] regarded the appearance of these cells as due to "axonal reaction." Marchi degeneration was present in the peripheral nerves.

Cole [3] gave a very full and detailed account of the changes he found in the nervous system of two patients. He also found acute cell degeneration in the Betz cells, in the cranial nerve nuclei and in the anterior horn cells of the spinal cord. In one case there was a slight atrophy of the tangential fibres in the cortex. In both cases there was extensive degeneration of the posterior columns of the spinal cord throughout its length. Degeneration of the pyramidal tract was also seen at all levels. The peripheral nerves and the vagus nerve all showed degeneration by Marchi's method. The muscles had undergone fatty degeneration. Cole considered the affection to be polyneuronal rather than polyneuritic.

Mott [24] examined the nervous system in two fatal cases of Korsakoff's syndrome. He found that the brains did not show obvious signs of cerebral wasting. The microscopic changes consisted in slight wasting of the tangential, supraradial and interradial fibres of the cerebral cortex; otherwise the fibre tracts were normal except in very severe cases in which there was degeneration in the posterior roots and columns of the spinal cord. There was acute chromatolysis of the Betz cells and of the anterior horn cells of the spinal cord. The cytoplasm of these cells contained an excess of pigment. Mott also found changes in the vessels in the cortex. Their walls were undergoing fatty degeneration, and around some vessels were hæmorrhages. Mott maintained that the changes he found in the brain were due to functional deterioration of the cortical neurones caused by a poison circulating in the blood, and that these changes were not necessarily permanent, but recoverable. Gudden [9] examined four cases pathologically. He found atrophy of the tangential fibres in the third frontal convolution; disappearance of the Nissl bodies from the large nerve cells in the cortex; thickening of the cortical blood-vessels with hyaline degeneration of their walls. Gudden considered the loss of tangential fibres the earliest and most constant lesion.

Marcus [20] studied the pathological changes in five cases. The acute cases showed different changes from the chronic cases. In the acute cases the lesions were confined mainly to the frontal region and to the deeper layers of the cortex. No degeneration of fibres was observed. Many small vessels in the cortex were thrombosed and the tissues around them stained badly; the nerve cells being degenerate and undergoing phagocytosis. The zona multiformis contained many degenerate cells. Degenerate cells were also seen in the corpus striatum. The spinal cord and nerves were not examined in the acute cases. In the chronic cases the brains were much atrophied. Most of the external layers of the frontal cortex were transformed into a reticulated tissue, the normal architecture of the cortex being hardly recognizable. Many newly-formed vessels were present, of which some were thrombosed. A few miliary necroses were present. The ganglion cells were disintegrated but little neuronophagia was to be seen. In the basal nuclei miliary necroses were observed. Marcus concluded that the outstanding lesion in Korsakoff's syndrome was a parenchymatous degeneration in the cerebral cortex. The changes were greatest in the deepest layer of the cortex, and only slight in the superficial layers, whilst the predilection of the process was for the anterior part of the frontal lobes.

The largest series of cases examined pathologically is that of Gamper [6], who examined the brains of sixteen patients who had died from chronic alcoholism with "Korsakoff's psychosis." In most cases the psychosis was of acute onset ending in death after eight to fourteen days. In three cases the patient lived for two months and in one case for nine months. Gamper found that the cerebral cortex was normal in all his cases. The most striking changes were seen in the mid-brain. Gamper described two types of lesion: (1) great proliferation of the endothelial and muscular walls of the blood-vessels with neuroglial overgrowth and secondary destruction of the nerve cells in the nuclei, especially of the inferior corpora quadrigemina and the corpora mamillaria; (2) irregular areas of porosis in which were thickened blood-vessels with proliferation of their endothelium. The latter type of lesion was found mainly in the central grey matter of the mid-brain. No inflammatory reaction was observed, and the nerve cells appeared healthy where they were not pressed upon by neuroglial overgrowth. Gamper considered that the disease process was a local elective one, not exclusively, but most severely incident upon, the vegetative nervous system. The spinal cords and nerves were not examined in this series.

Case Reports with Pathological Examination.

Case 1.—S. H., a single man, aged 40, was admitted to the National Hospital under the care of Dr. Riddoch on October 25, 1930. The history obtained from the patient was unreliable owing to obvious gross lapses of memory, especially in relation to intervals of time. The patient was incapable of making spontaneously any but the simplest possible statements. Direct questioning elicited the following story: For three to four weeks past he had had practically no food, but had been drinking large quantities of whisky. He spoke as if he realized that his present trouble was due to this. At the end of the orgy intermittent pains were felt all over the body, particularly in the legs. The character of the pains was not described, but was definitely said not to be "shooting" in character. The patient also complained of loss of appetite, of general "shakiness" and of passing "smoky" urine. Time intervals were given, but they were hopelessly contradictory. The onset of symptoms was probably from three to five weeks before admission. Two weeks before admission, he began to "go off his legs." The arms too became progressively weaker, but he said that he was actually confined to bed only one day before he came into hospital.

Past illnesses: none except a left mastoidectomy fourteen years before. On examination, the patient was seen to be a flabby-looking, obese, middle-aged man. His face was pale and puffy, but there was no local or generalized

œdema. Speech was slurred. The mental state was apathetic. The patient did not appear cognizant of the gravity of his condition. He was co-operative and correctly orientated when first examined and had no delusions or hallucinations. There was no obvious confabulation or confusion at this time, but memory was poor for the details of his history and his statements were unreliable owing to self-contradiction.

The optic discs were normal. The pupils were slightly irregular in outline and reacted sluggishly to light, both direct and consensual. The corneal reflexes were both absent. There was deafness on the left side. Both trapezii were very weak: hardly any contraction could be obtained on either side. Generalized tremor of the tongue was present.

The arms and legs were almost completely powerless and lay flaccidly on the bed. Any movement that was possible was interrupted and short-lived. Some power of grasp and of extension of the fingers was retained. The feet could only just be moved, but plantar flexion was much better than dorsiflexion. All the limbs were toneless. There was no obvious atrophy, fibrillation or tremor. The patient could raise his head off the bed, but the abdominal muscles did not contract when this movement was carried out.

Sensation was difficult to test as the patient was an unreliable witness. There was, however, a diminished response to stimulation by pin-prick and cotton-wool on the legs as compared with the arms. Hypalgesia of the legs was greater peripherally than proximally. Vibration sense was also diminished in the legs as compared with the arms. Deep pressure sensibility was hyperacute in both arms and legs, especially in the calf muscles. The deep and superficial reflexes were all absent.

No abnormalities were detected in the cardiovascular and respiratory systems. There was some tenderness to moderate palpation in the right hypochondrium, but no rigidity. The liver margins were normal to percussion.

On the day after admission the patient became confused and disorientated. One minute he said that he had walked up to hospital that day, the next that he had been in hospital three or four days. He also became excitable and restless. He admitted that he had drunk ¾ bottle of whiskey a day but said that he had stopped drinking "a long time ago." (A message from his private doctor stated that he had been drinking a bottle of whiskey a day as recently as the day before admission.) Next day the patient became more confused, rambling in his statements and violent. His temperature rose to 102° F. He died very suddenly on October 28, three days after admission.

A post-mortem examination was performed thirty-six hours after death by Dr. J. G. Greenfield.

Post-mortem notes.—The body was that of a well-nourished man with no evidence of œdema. On removal of the brain and spinal cord the brain appeared pale and œdematous. Several peripheral nerves were removed for section. The lungs were œdematous and congested. The heart appeared healthy but flabby. The liver was pale with a central pallor in each lobule which apparently represented a fatty change. The kidneys and spleen appeared normal. Nothing remained of the suprarenals but empty capsules.

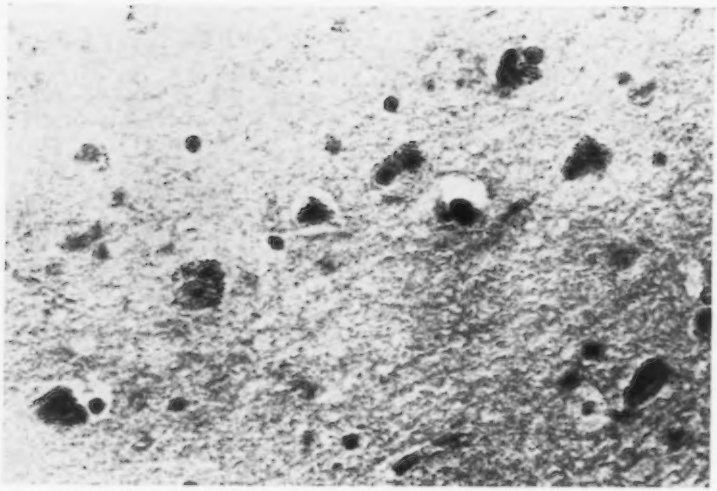
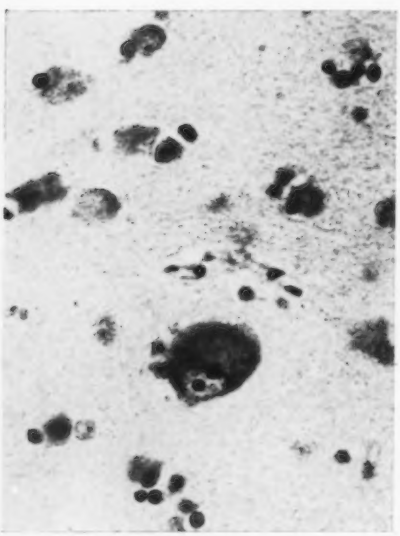
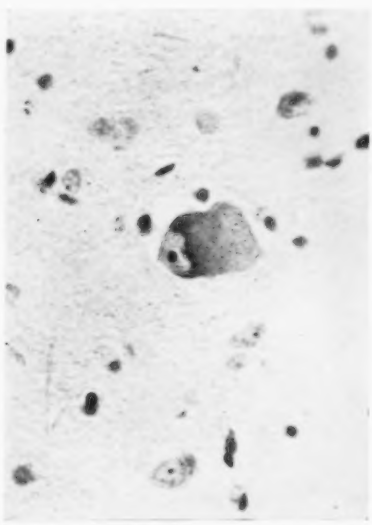


FIG. 1.—Section from prefrontal cortex of *Case* 1 stained with Scharlach R. and hæmatoxylin, to show the large accumulation of lipochrome in the nerve-cells.





FIGS. 2 and 3.—Sections from the motor cortex of *Case* 4. Two Betz cells are seen undergoing chromatolysis. In fig. 2 accumulations of lipochrome granules are visible in the Betz cell and in one or two of the smaller nerve cells. (Celloidin section, stained with toluidin blue.)

To illustrate paper by Carmichael and Stern.

Microscopical examination.—Sections of the liver showed advanced fatty degeneration of the liver cells with early periportal fibrosis.

The heart muscle appeared normal.

The nervous system in all our cases was examined by a variety of staining methods. The following methods were employed on every case. Scharlach R., Bielschowsky, toluidin-blue (Nissl), Cone and Penfield's modification of Hortega's method on frozen sections; Weigert-Pal or Loyez' stain for myelin, toluidin-blue, Marchi, hæmatoxylin with van Gieson's counterstain on celloidin sections. In three cases Marinesco's method for the demonstration of senile plaques was used. The cerebral cortex when stained with Scharlach R. presented a striking appearance. Heavy deposits of a lipoid which stained bright orange with Scharlach R. surrounded nearly all the blood-vessels in the grey matter and most of those in the white matter. Both the large and the small nerve cells in the prefrontal and motor areas contained numerous droplets of a lipoid which gave a similar coloration with Scharlach R. to that around the blood-vessels. Deposits of this lipoid were also present in the neuroglial cells of the superficial layers of the cortex in these two areas. The lipoid appeared in many situations almost completely to fill the cell body. This is shown in fig. 1. The amount of lipoid was greatest in the cells of the prefrontal area; there was much less in the cells of the motor area. The size of the droplets in the nerve cells was rather larger than in the deposit which ringed the blood-vessels. Certain solubility tests and staining reactions which Hurst [12] used in his study of the lipoids in neuronic degeneration were carried out in an attempt to ascertain the nature of this lipoid. Before we consider these tests it is necessary to state that the deposits of lipoid in the nerve-cells and around the vessels occurred only in the cerebral cortex and in the olivary nuclei in the medulla (where a large amount of lipochrome is normally present). We could not find such deposits in the cells of the mid-brain, hypothalamic nuclei, pons or medulla. For comparison with the sections from this case we subjected to the same solubility tests at the same time sections from the cerebral cortex of a senile patient in which much lipochrome pigment was present in the Betz cells.

We found that immersion in absolute alcohol or acetone for twenty-four hours had no appreciable effect on the staining properties of the unknown lipoid; thereafter it still stained bright orange. Similarly, immersion in absolute alcohol for twenty-four hours after a preliminary treatment for twenty-four hours with saturated zinc sulphate failed to affect the staining reaction of this lipoid with Scharlach R. These tests indicated that the lipoid which we observed did not contain either true fats or fatty acids. Immersion in acidified absolute alcohol and ether for twenty-four hours had some effect on subsequent staining with Scharlach R. The coloration of the lipoid was paler and more yellow than in untreated sections; but not more so than in the sections which we used as controls and which we knew contained lipochrome. As the unknown lipoid was not doubly refractile and stained with Kultschitsky's hæmatoxylin, after five days' mordanting, we concluded that it

possessed all the properties of lipochrome, as detailed by Hurst, and was in fact that substance. Although lipochrome itself is insoluble in a mixture of acidified alcohol and ether, the fact that it stains more faintly with Scharlach R. after treatment with these fat solvents calls for some explanation. That given by Greenfield and Holmes [8] in the section on lipoid deposits in their paper on Amaurotic Familial Idiocy seems in accordance with what is known about the mode of action of Scharlach R. This dye does not act as a stain but becomes dissolved in any fatty substance present. According to Greenfield and Holmes, although the lipochrome is not dissolved by alcoholic solvents the dye is unable to act owing to the removal of normal myelin by these solvents. The rapid wash in 70 per cent. alcohol which the sections are given after immersion in Scharlach R. is sufficient to dissolve out the dye from the nerve cells when no other parts of the sections are holding it. The resistance of lipochrome to fatty solvents may be gauged from its presence in celloidin sections stained by the Nissl method, as greenish-grey granules. We observed these granules in the nerve cells of the cortex, particularly of the frontal region, in this case; they corresponded to the droplets of lipoid seen in frozen sections with Scharlach R.

The appearance of the nerve cells in the cortex was relatively normal. Certain large nerve cells in the prefrontal cortex and one or two Betz cells in the motor area had eccentric nuclei which lay against the cellular membrane and were oval or crescentic in shape, but these abnormal cells were few in number compared with those in our other cases. There was no perivascular infiltration or satellitosis and the blood-vessels of the cortex appeared healthy. The cortical fibres were well myelinated.

We paid particular attention to sections of the thalamic nuclei and corpora mamillaria in this case, as Gamper has reported a degeneration of their cells in Korsakoff's syndrome which he considers an essential lesion. Although we found that all the nerve cells in the thalamic nuclei and corpora mamillaria were rounded or had only one or two short processes, whilst their nuclei were slightly eccentric and the Nissl granules were in "clumps" rather than in a regular pattern, yet two normal corpora mamillaria from cases in which the sole lesions were in the spinal cord presented exactly the same appearance. We therefore concluded that the appearance of these cells in the alcoholic case could not be accepted as evidence of degeneration of the cells. We have been confirmed in this opinion by illustrations of the normal histology of the corpora mamillaria and thalamic nuclei in the recent "Handbuch der Mikroscopischen Anatomie des Menschen." The basal ganglia, mid-brain, pons and medulla did not show any abnormalities.

The only departure from the normal which we observed in the spinal cord was in Nissl sections at the level of the fifth lumbar segment and from the cervical enlargement. In these sections the anterior horn cells showed early chromatolytic changes.

The only peripheral nerve available for section was a small portion of the popliteal. No interstitial changes were seen in sections of this nerve stained

by hæmatoxylin and van Gieson, but Kernohan's modification for celloidin sections of Bielschowsky's method showed degeneration of many axis cylinders. A portion of muscle from the calf was sectioned. The muscle-fibres appeared normal in size and shape. There was no increase in the number of sarcolemmal nuclei and no fibrosis.

Case 2.—R. C., married man, aged 48, was admitted to the National Hospital under the care of Dr. Riddoch, on October 25, 1928. He complained of weakness and pains in the limbs and loss of appetite. In addition, the history was obtained from a relative that defective mental concentration had been present for the past ten years, gradually increasing in severity, and culminating during the ten days prior to admission to hospital in systematized delusions and fabrication of elaborate stories. Two months ago the legs suddenly "gave way" and the patient had been unable to walk since. The pain in the legs was very severe and much worse on movement. He had taken very little food for some weeks. Incontinence of urine and fæces had been present for some days.

Sixteen years ago the patient had had malaria whilst out East and was sent home with "alcoholic paralysis" of the legs. He had walked with two sticks ever since. For the past ten years, up to June, 1928, he had drunk 1 to 1½ bottles of whisky a day and since then even more. He had had no other illnesses.

On examination the patient was found to be an obese unhealthy looking individual. He was not drowsy but very inattentive and slow-witted. He had varied and complicated delusions about his surroundings and associates, and was constantly under the impression that he was elsewhere than in hospital. Memory was poor for recent events, but much better for distant ones. The patient fabricated elaborate stories in order to get his own way. Speech was blurred and slovenly. There was a gross facial tremor.

Cranial nerves.—The optic discs were normal. The pupils reacted well to light, both direct and consensual, and to accommodation. Ocular movements were normal and the fields were full. Both corneal reflexes were present and equal. There was a generalized facial tremor, and generalized tremor of the tongue was also present.

The musculature of the limbs was poorly developed. Power in the arms was very weak, especially in the fingers and wrist. The patient could raise his head from the bed, but not his shoulders. Power in the legs was almost completely lost. There was complete double foot-drop with an early contracture of the calf muscles.

At the time of examination the patient did not complain of spontaneous pain or paræsthesiæ; but deep pressure on any group of muscles in the limbs gave rise to severe pain. There was peripheral diminution of sensibility to pin-prick and cotton-wool in all limbs and vibration sense was abolished in the legs. The arm, knee, ankle and abdominal reflexes were absent on both sides. The plantar responses were flexor.

The heart was not enlarged. The apex-beat could be neither felt nor seen.

The heart sounds were distinct and the rhythm "tic-tac." The blood-pressure was 110 systolic, 80 diastolic. The respiratory and alimentary systems appeared normal. Progress notes on October 29 stated that the patient was much troubled by insomnia and required nightly doses of 2 drm. of paraldehyde to induce sleep, which even then was fitful. Much of the night was passed in a mild mumbling delirium. Disorientation was not quite complete, although from time to time the patient insisted that he was either at home or abroad.

A progress note on November 5 reported that the patient had become very helpless. He was then sleeping badly even after paraldehyde. His mental condition was more abnormal in that his fabrications had reached a stage of astonishing complexity, and were completely free from any element of self-criticism. From this time the patient went downhill rapidly and died on November 14.

A post-mortem was performed thirty-six hours after death by Dr. J. G. Greenfield.

Post-mortem notes.—The body was that of a big fat man. The muscles of the arms below the elbow and of the legs below the knee were considerably wasted. Double foot-drop was present. On removal of the brain and spinal cord the veins over the vertex were seen to be considerably distended and the sulci were widened. There was some congestion of the veins around the theca in the lumbar region. No disease was evident in the cerebral vessels. The left lung was congested at the base. The heart was flabby and dilated, but the valves appeared normal. The aorta appeared remarkably healthy. The liver was small and pale. The kidneys and spleen were congested. The supra-renals appeared healthy. Portions of numerous nerves and muscles were taken for section.

Microscopical examination.—In sections of the liver an intense fatty degeneration of the epithelial cells was seen. Very few healthy cells remained. There was no periportal fibrosis. Fatty degeneration was also present in the heart muscle. In the kidneys there were degenerative changes in the convoluted tubules, many of which were completely disintegrated. The lungs were much congested. Many "heart failure" cells were present.

In the *nervous system* the most striking changes were seen in sections of the cerebral cortex stained by Scharlach R. method. Nearly every nerve cell, both large and small, contained numerous droplets of a lipoid substance which stained deep orange with the dye. In the more superficial layers of the cortex lipoid was present in and around neuroglial cells, but in the microglia rather than in the protoplasmic neuroglia. Considerable quantities of this lipoid, together with a large number of compound granular corpuscles, were found around the majority of blood-vessels in the cortex. No lipoid was seen surrounding the blood-vessels in the white matter. The region of the cortex in which most lipoid was present in the nerve cells was the prefrontal region. The Betz cells contained a large quantity of lipoid, but the smaller nerve cells in the motor region were comparatively free from the deposit. In the temporal and occipital regions, only the large nerve cells contained much lipoid, although there was some accumulation of lipoid around the vessels.

We employed the same solubility tests on sections of the cortex as we did in Case 1 in order to ascertain the nature of the lipoid; and we obtained the same results. After prolonged immersion in an acidified solution of absolute alcohol and ether it was still possible to obtain a bright yellow coloration of the lipoid with Scharlach R., not as brilliant certainly as in untreated sections, but quite as bright as the lipochrome pigment in control sections. We therefore considered that the lipoid present in the cortical cells of this case was also lipochrome, i.e., not an abnormal product of cellular metabolism, but a normal product present in abnormal quantities.

This production of abnormal amounts of lipochrome appeared to be confined to the cells of the cerebral cortex. The cells of the basal ganglia, mid-brain, pons and medulla did not contain more than a few granules of lipochrome, not comparable with the amounts present in the cells of the cortex.

In sections stained by the Bielschowsky method the neurofibrils of the cortical nerve cells seemed to be pushed to the periphery of the cells by the lipochrome deposits, but the intracellular course of the fibrils was easily discernible and they appeared normal. Neither by this method nor by that of Marinesco could we demonstrate senile plaques in the cortex.

The nerve cells in the prefrontal and motor areas of cortex, when stained by the Nissl method, displayed changes common to all our cases, but varying in the degree of severity. These changes involved not only the large nerve cells in these areas but, in this case, the smaller nerve cells in both areas, though particularly in the frontal region. Although the size of the Betz cells made the alteration in structure more obvious in them the cells in the prefrontal region were certainly as much, if not more, affected than those in the motor region. The affected cells appeared to be undergoing acute chromatolysis. Their processes were lost or shortened, their nuclei were crescentic in shape and lay eccentrically, often just under the capsule, whilst the Nissl granules were either confined to the periphery of the cells or had disappeared. But nowhere did we observe any evidence of satellitosis or phagocytosis of these apparently degenerate cells. Neither could we discover any "ghost cells" resulting from partial disintegration of the cells.

The hæmatoxylin and van Gieson stain revealed an intense engorgement of the cortical vessels, especially in the grey matter. The cortical arteries were slightly thickened. No perivascular infiltration was present in either the grey or the white matter.

The microglia appeared normal by Hortega's method. When stained by the Kultschitsky-Pal method the superficial tangential fibres of the frontal cortex appeared to be less numerous than normal. In part of their course these fibres displayed bulbous swellings, indicating an early stage in degeneration.

We could find no pathological changes by any method in the basal ganglia, the mid-brain, pons or medulla.

The spinal cord in the region of the cervical and lumbo-sacral enlargements exhibited severe axonal reaction. Numerous cells in the anterior horns were rounded and vacuolated, and contained either eccentric nuclei or were devoid

of nuclei. There was no evidence of tract degeneration in the spinal cord at any level. The anterior nerve roots at all levels of the cord stained more faintly with Loyez' myelin stain than did the posterior roots.

The following peripheral nerves were examined: sciatic, median, ulnar, radial and internal cutaneous. The majority of the fibres in all these nerves were seen to be degenerating when stained by the Marchi-Busch method. The Weigert-Pal method demonstrated that many fibres had already reached an advanced stage of degeneration. In the sciatic nerve there was a slight perineural infiltration with small round cells. In the radial nerve early interfibrillar fibrosis was seen but no cellular infiltration. The other nerves did not show any reaction of the interstitial tissues. The degenerative process appeared to be a simple parenchymatous degeneration of the nerve fibres.

The biceps brachialis, tibialis anticus, soleus and biceps femoris muscles were examined. Many fibres of the soleus muscle had atrophied. There was no fibrous or fatty replacement of muscular tissue. No increase in sarcolemmal nuclei was noted. The gastrocnemius, tibialis anticus and biceps femoris all contained some atrophied fibres, but not so many as the soleus. The size of the fibres in the biceps brachialis appeared normal.

For the clinical and post-mortem notes on the two following cases we are indebted to Dr. W. Gordon Sears, Assistant Medical Officer at the Mile End Hospital.

Case 3.—A. L., a married woman, aged 43, was admitted to the Mile End Hospital on November 21, 1929. She complained of loss of power in the legs, especially on attempting to walk upstairs, the duration of this symptom being five weeks. She had had pains in the legs "on and off for years" and four years previously had been treated for this symptom and for "stomach-ache" in St. Andrew's Hospital. The pains in the legs became worse when the power in them grew weak. For two weeks prior to admission to Mile End Hospital the patient had been confined to bed and had been vomiting "on and off." Shortly before admission to hospital there had been loss of sphincter control. A relative gave the history that the patient had shown mental symptoms after the suicide of her father a short time previously. She had been a heavy whisky drinker at times, but was stated not to have been ever obviously drunk. The family history was essentially negative; she had had no children and no miscarriage. There had been no serious illnesses except a laparotomy and left ovariectomy.

On examination the mental state of the patient was found to be dull. She displayed little interest in her surroundings and apparently had some loss of memory, and some indefinite delusions about her husband.

The pupils were slightly eccentric and reacted sluggishly to light. The optic discs were normal. Nystagmus was present on looking to right and left and there was a slight weakness of the right external rectus muscle. The patient had been deaf for some time. There was bilateral wrist-drop with great weakness of the grip on both sides.

The power of movement of both legs was very poor. The calf-muscles were tender on deep pressure and there was diminution of sensation to pin-prick on the legs. Both knee- and ankle-jerks were absent. The plantar responses were doubtful.

No abnormalities were detected in the alimentary or respiratory systems. The heart was not enlarged but a systolic bruit could be heard over all areas. There was some pallor of the mucous membranes. A blood-count gave the following result: red blood-corpuscles, 4,270,000; hæmoglobin, 56 per cent.; colour index, 0·7; white blood-corpuscles, 17,480. Differential count: polymorphonuclears, 70 per cent. (12,236); lymphocytes, 16·5 per cent. (2,884); large hyalines, 13·5 per cent. (2,360). The patient died rather suddenly on November 24, 1929, three days after admission.

Post-mortem findings.—The brain and spinal cord showed no macroscopic abnormality. A small portion of the musculo-spiral nerve was removed for section. The thoracic organs all appeared healthy. The stomach presented the appearance of a chronic gastritis. The liver was pale and was evidently undergoing fatty degeneration. The gall-bladder and spleen appeared normal. The kidneys and bladder were congested, but otherwise normal.

Microscopical examination.—On section of the liver an intense fatty degeneration of liver cells was noted. A similar degeneration of the cells of the heart muscle was found, together with an early interstitial fibrosis.

In the *nervous system*, sections of the frontal and motor regions of the cerebral cortex when stained by Scharlach R. showed large accumulations of lipochrome pigment in the Betz cells and in most of the large nerve cells.

When stained with toluidin blue, several Betz cells were seen to possess eccentric nuclei and peripherally distributed Nissl granules, but the majority of the nerve cells in the cortex in this case appeared healthy. A few, however, in the motor region were surrounded by satellite cells, which appeared to be engulfing them. These satellite cells were shown by Cone and Penfield's modification of Hortega's method to be microglia. Most of the microglial cells were normal in shape, but one or two elongated forms with terminal processes only were seen. These abnormal forms occurred only in the motor area; we did not find them in the frontal region. No perivascular infiltration was observed, but the vessels in both the white and the grey matter were thickened. The cortical fibres were well myelinated. The neurofibrils of the cortical nerve cells appeared normal and we could not demonstrate senile plaques by either the Bielschowsky or the Marinesco method. No abnormalities could be detected in the basal ganglia, mid-brain, pons or medulla.

The sole pathological change we found in the spinal cord was early chromatolysis of a few anterior horn cells in the lower lumbar segments. The only peripheral nerve available for examination in this case was a small portion of the musculospiral. There was no evidence of degeneration in the part examined by the Marchi method, and no cellular infiltration or fibrosis was seen in that stained with hæmatoxylin and van Gieson. No muscle was examined in this case.

Case 4.—A. A., a married woman, aged 41, was admitted to the Mile End Hospital on August 29, 1930. She complained of the loss of use of her legs, pain in the shoulder and legs, and some numbness of the hands, feet and legs. The duration of all these symptoms was given as two weeks. The patient had been a regular spirit drinker "for some time." The family history was essentially negative: she had had eight children.

On examination the patient was found to be dirty in her habits. She was disorientated in time and space (gave day of week and name of hospital wrongly). She thought that the examiner had been to see her at her home and that he had met her son (pseudo-reminiscence). She was irrational and very noisy.

The pupils reacted sluggishly to light. The optic discs and the other cranial nerves appeared normal. Power in the arms was good, and there was some dubious diminution of sensation to pin-prick (patient was a poor witness). The arm-jerks were brisk. Power in the legs was poor. There was apparent loss of sensation to pin-prick over the whole of the lower limbs and over the trunk as high as the level of the nipples. The knee- and ankle-jerks were lost on both sides. The plantar responses were flexor.

The heart was not enlarged, but the first sound at the apex was accentuated. The heart sounds were obscured by coarse rhonchi all over the chest. The liver was just palpable below the costal margin. Blood Wassermann reaction was negative. The patient became more irrational and more noisy day by day and went downhill rapidly. She died on September 12, 1930.

Post-mortem findings.—Well-marked post-mortem staining was present and there was a slight redness of the skin over the sacrum.

On removal of the brain and spinal cord the arachnoid membrane covering the brain was more adherent than normal. There was some flattening of the convolutions and the brain appeared œdematous. The spinal cord presented no macroscopic abnormality. The cerebral vessels appeared healthy.

The lungs were congested but otherwise healthy. A few enlarged glands were present at the roots of the lungs. The heart was of average size and appeared normal except for a slight thickening of the mitral valve. The stomach was in a condition of chronic gastritis. The mucous membrane was atrophic and a number of small hæmorrhages were present in the wall. The liver was not enlarged but was very pale, due to fatty changes. The spleen was soft and diffluent. The kidneys and pancreas were healthy.

Microscopical examination.—Sections of the cerebral cortex stained with Scharlach R. presented the same appearance as did the cortex in the three cases previously described. The large nerve cells, particularly in the frontal cortex, were filled with a lipoid material which gave the solubility reactions of lipochrome. The smaller nerve cells in the frontal area and the Betz cells in the motor area, did not contain so much lipochrome as the cells in the frontal region, and the deposition of lipochrome in the glial cells of the superficial layers of the cortex was not so obvious as in our other cases.

The intracellular neurofibrils appeared normal by the Bielschowsky method,

though in the frontal region they were displaced to the periphery of the cells by the lipochrome. We could nowhere in the cortex find any senile plaques.

When stained by the Nissl method, most of the large nerve cells in the prefrontal and motor areas were found to be in a condition of acute chromatolysis. Many of the small nerve cells in these areas presented the same appearance. The affected cells were rounded, their processes being shortened or lost: their nuclei were of bizarre shape and situated at the extreme periphery of the cell, just under the capsule, whilst the Nissl bodies were either completely lost, or more commonly arranged in finely granular masses at the periphery of the cell. Examples of these cells are well seen in figs. 2 and 3.

The alterations in structure of the nerve cells of the cortex in this case were more severe than in any of our other cases. But we could nowhere determine any evidence of neuronophagia or satellitosis: neither did the hæmatoxylin and van Gieson stain reveal any perivascular infiltration or changes in the blood-vessels. The lesions in the brain appeared to be confined entirely to the nerve cells of the cerebral cortex, since the Weigert-Pal method did not demonstrate any loss of myelinated fibres in the cortex and the midbrain, the pons and medulla showed no abnormality by any staining method. The spinal cord was stained with Scharlach R. and with Loyez' stain for myelin, but neither of these stains revealed degeneration of fibre tracts at any level of the cord.

In the fifth lumbar segment, several anterior horn cells were seen by the Nissl method to be chromatolytic. At other levels of the cord these cells appeared normal.

The median, ulnar, sciatic and posterior tibial nerves were examined. Early degeneration was found in all these nerves by the Marchi method, but more advanced degeneration was present in the posterior tibial than in the other nerves. In the ulnar and median nerves the perineural spaces contained a small number of lymphocytes and large mononuclear cells. In the posterior tibial nerve, no infiltration with cells was observed, but there was slight proliferation of the cells of the sheath of Schwann.

The gastrocnemius and flexor digitorum communis muscles were examined. The fibres of the latter muscle were normal in size and shape. Those of the gastrocnemius were small and atrophic, the average size being 20 to 25 μ. There was an increase in the number of sarcolemmal nuclei, but no fibrosis or other interstitial change.

Case 5.—R.S., a married woman, aged 43, was admitted to St. Bartholomew's Hospital, under the care of Professor Fraser. The patient was incapable of giving a satisfactory history as she was in a somewhat stuporous condition, not realizing where she was, nor the time. Even to direct questioning no satisfactory or consistent replies were forthcoming. The relatives supplied the following history:—

Eighteen months previously the patient had been operated on for a pelvic condition. Following this she never quite recovered and "owing to her heart

being weak " took brandy. This stimulant was changed to " bitters and ale " six months before admission. A few weeks after the alteration in fluid diet she began to have difficulty in passing water. This was followed by weakness in the legs, dropping of the wrists and weakness of the arms. Brandy was again resorted to as a stimulant. For a few days immediately prior to admission she had had diarrhœa. Mentally she had only become affected in the last few weeks of her illness ; she had become forgetful, unreliable, and eventually drowsy. No history of pains could be obtained from the relatives. She had not had any serious illness before this and had borne four healthy children.

On examination the patient was found to be a pale, well-nourished female who was an unreliable historian of her own illness. She was edentulous, had a furred tongue and pale mucous membranes. The pupils were contracted, the right being larger than the left ; both reacted to light and on accommodation. The fundi were normal. There was a divergent strabismus and on looking to the right or left a definite, though ill-sustained, nystagmus was present. The remaining cranial nerves were normal. There was definite wrist-drop on both sides with very marked weakness of the extensors and some weakness of the flexure of the wrist and fingers. The muscles of the fore-arm and arm were exceedingly tender to palpation. Below the elbow there was slight wasting of the muscles but no fibrillation was seen. The legs showed definite wasting, especially below the knee, which was associated with weakness of the muscles, more marked in the dorsiflexors than in the plantar flexors of the feet. The calves were exquisitely tender on deep palpation, and the skin and superficial tissues were tender up to the level of the umbilicus. All the deep tendon reflexes were absent even on reinforcement, except the right biceps reflex. The abdominal reflexes were absent ; the plantar responses flexor. Sensation was difficult to test owing to patient's mentality, but there appeared to be some loss to superficial sensibility in both arms and legs, chiefly at the periphery.

The chest movements were normal and no clinical evidence was obtained of changes in the lungs. The heart was dilated, the apex-beat lying outside the mid-clavicular line. The heart sounds were normal. The liver was enlarged, three fingers' breadth below the costal margin, and was tender. The spleen was not palpable. There was no excessive pigmentation of the trunk or hyperkeratosis of the hands or feet. The urine contained a trace of albumin but no sugar or acetone.

During the three days which elapsed between admission and death, the temperature remained normal, the pulse-rate about 110 and the respiration rate at 20 to 26. At no time was any sugar found in the urine and tests for arsenic were negative. The patient's mental condition rapidly became worse until she was unable to answer any questions whatsoever. The condition of her nervous system remained the same until death.

After death the relatives furnished further details of the mental changes, which included forgetfulness, a tendency to uncleanliness and disregard for her personal appearance.

From the history, unsatisfactory though it was, together with the results of the clinical examination, a diagnosis of Korsakoff's syndrome was made.

A post-mortem examination was carried out by one of us (E. A. C.) within twenty-four hours of death.

The body was that of a well-nourished woman. The heart was surrounded by much sub-pericardial fat. The heart muscles looked pale, but except for dilatation of the left ventricle, the chambers and valves were normal. The aorta was covered with atheromatous patches, especially in the region of the arch. The liver was large, pale, coarsely cirrhotic, and on section obviously fatty. The spleen and kidneys were normal and no changes were observed in the suprarenal bodies. On removal of the brain and spinal cord no gross abnormality was observed. The cerebral blood-vessels appeared healthy. Portions of both sciatic nerves, both popliteal and internal tibial nerves were removed for section. Unfortunately no nerves were removed from the arms.

Microscopically, considerable changes were found in the internal organs as well as in the central and peripheral nervous system. The heart muscle showed fatty infiltration. In the aorta marked fatty changes were present in the intima, with definite atheromatous plaque formation. The vasa vasorum did not show any marked changes in their endothelium. The kidneys had slightly thickened capsules, but the glomeruli, the tubules and the blood-vessels all appeared normal. The spleen was mildly congested but did not exhibit any gross abnormality. The suprarenal bodies were normal. The liver showed a well-marked cirrhosis of the multilobular type; the liver tissue surrounded by fibrous bands was fatty, so that when stained with Scharlach R. the sections appeared to consist of masses of fatty substance. Scattered amongst the areas of fibrosis were small collections of round cells and in the immediate vicinity of the fibrous tissue new bile duct formation was evident.

Slices from the frontal, motor, parietal, occipital and temporal gyri were taken for microscopical examination. Portions of the mid-brain, pons, medulla and the corpus striatum were also sectioned. The changes in the frontal, parietal, occipital and temporal gyri were all similar. The most easily discernible abnormality was a fatty change in the endothelium of the small blood-vessels entering the cortex. There also appeared to be an excessive quantity of lipoid material which stained orange with Scharlach R. in the neuroglial cells immediately beneath the pia mater. These lipoid changes were more evident at the base of the sulci. The neuroglial cells appeared normal by Cajal's gold-sublimate impregnation method. No evidence was obtained that any alteration had taken place in the "sucker feet" attached to vessels with fatty endothelium. The nerve cells were apparently healthy as demonstrated by the following methods of staining: Scharlach R., Da Fano's neurofibril stain, and Nissl's stain. In the prefrontal cortex the white matter immediately subjacent in the cortex contained in several sections a larger number of compound granular corpuscles than are seen in normal brain tissues. The myelin, however, in sections stained by the Weigert-Pal method and by Scharlach R. appeared quite normal.

More interesting changes were found in the motor cortex. The Betz cells appeared as numerous as normal, but in many the nuclei were eccentric, whilst

in others the lipoid material appeared excessive. In sections stained for Nissl granules an occasional cell was found in which the granules were arranged around the periphery. The neurofibrils appeared normal by Da Fano's method. The neuroglial elements were undisturbed by the pathological process, although immediately beneath the pia mater, as in the rest of the cortex, the neuroglial cells contained large quantities of lipoid material. The myelin appeared unaffected and there was no excess of compound granular corpuscles.

Sections from the corpus striatum showed no demonstrable lesion of the nerve cells of the thalamus, caudate, putamen or globus pallidus. The nerve cells of the thalamus adjacent to the ventricle appeared unduly laden with a fatty substance staining orange with Scharlach R., whilst in the subependymal region there was an excess of neuroglial cells containing lipoid material. In this region also a fair number of microglial cells were laden with fat. This suggested a degenerative process. In one section thrombosis of a small vessel was found, with some perivascular softening. This may have accounted for the fat-laden microglial cells seen in other sections. The neuroglia as well as the ependyma appeared normal. The choroid plexus exhibited fatty changes, the choroidal cells themselves containing fat globules, whilst the endothelium of the blood-vessels gave the reaction for fat with Scharlach R.

In the spinal cord maximal abnormalities were found in the cervical and lumbo-sacral enlargements. The anterior horns appeared to suffer most by the pathological process. The large anterior horn cells contained a large excess of fatty substance, and in many instances the fatty material lay outside the cell in its immediate neighbourhood. In such instances the nuclei were displaced eccentrically and the Nissl granules stained poorly and were grouped around the periphery. In the lumbar region many of the anterior horn cells had neither nuclei nor Nissl granules and only a faint outline of the cell was visible. Around these "ghost cells" there was no evidence of an acute reactive process. No changes were found in the posterior horns. The tracts of the spinal cord appeared normal when stained by the Scharlach R. and Weigert-Pal methods. Several pieces of the spinal cord were also examined by the Marchi-Busch method; in none of the sections examined by this method was there any evidence of early degenerative changes in the myelin. The anterior and posterior roots appeared normal by all staining methods. In some of the sections the endothelium of the smaller blood-vessels contained fat, but in no sections was a thrombosed vessel encountered.

Unfortunately the medulla, pons and mid-brain were damaged at the post-mortem. But in sections taken from various levels no changes could be demonstrated in the nerve tracts. The oculomotor nuclei were satisfactorily demonstrated and appeared normal: the lower cranial nerve nuclei were not demonstrated in the sections.

The following peripheral nerves were examined microscopically: Both sciatic nerves, both internal popliteal nerves and both anterior tibial nerves.

Definite degeneration of the anterior tibial and popliteal nerves was seen in

sections stained with Scharlach R. The myelin sheaths, especially those of the larger nerve fibres, were broken up into globules which stained either intensely red or orange with Scharlach R. Similar sections stained by the Marchi-Busch method showed fatty changes, though these were not nearly so evident as with the Scharlach R. stain. Weigert-Pal sections showed obvious fragmentation of the myelin, but in no case complete demyelination. There was a similar degeneration, though of much lesser degree, in the sciatic nerves. In no section was there any evidence of an inflammatory reaction. No cellular infiltration of the nerves whatsoever was found. Pieces of the gastrocnemius and anterior tibial group of muscles were examined, but no abnormalities were detected.

Discussion on the Pathology of Korsakoff's Syndrome.

The lesions which we found in our five cases agree to some extent with those recorded by other observers. The changes in the nerves and in the spinal cord we do not propose to discuss in any detail as they present only the well-known features of a degenerative parenchymatous neuritis with consequent degeneration of anterior horn cells in the spinal cord. But even in the most chronic case, Case 2, in which symptoms of neuritis had been present for sixteen years, we could find no evidence of degeneration of any tracts in the spinal cord. Most of the cases hitherto recorded have shown degeneration of the posterior columns even with a history of short duration.

The lesions in the brain were confined to the cerebral cortex, except in Case 5, in which slight changes were present in the thalamus. The lesions were entirely incident upon the cells; no tract degeneration could be determined, but in the most chronic case there was slight atrophy of the most superficial tangential fibres in the frontal cortex.

The widespread deposit of lipochrome material in the nerve cells and neuroglial cells in the cortex was the most remarkable feature in our cases. This deposit has not, as far as we can trace in the literature, been described before in Korsakoff's syndrome. In three of our cases the lipochrome was particularly heaped up in the nerve cells of the prefrontal cortex. In one case the cells of the thalamus were loaded with lipoid. Deposits of lipochrome around blood-vessels and in their walls were common. In one case there was a gross fatty change in the endothelial lining of the cortical blood-vessels; in the other cases no changes could be seen in the walls of the vessels themselves, although heavy deposits of lipoid with many compound granular corpuscles surrounded them. This deposit of lipoid, which by solubility tests we have shown to be lipochrome, is not a specific lesion. Similar deposits occur

in the nerve cells of senile patients and of patients dying from prolonged, exhausting diseases, but although we sectioned the brains of several senile patients and of patients who had developed psychoses during life, we could not demonstrate in them any accumulation of lipochrome in the neuroglial or microglial cells, nor was there such an amount present in the nerve cells as we found in our cases of Korsakoff's syndrome.

The only cases which we have been able to trace in which similar widespread deposits of lipochrome have been described are cases of pellagra. Kozowsky [16], in his review of the pathology of pellagra, drew attention to the enormous amount of yellow pigment he observed in the cortical nerve cells in Nissl preparations of the cortex. Winkelman [33] reported a series of cases of pellagra in which the chief pathological features were the accumulation of lipochrome in the nerve cells and glial cells of the cortex, especially in the frontal region, with fatty degeneration of the endothelium of the cortical vessels, a "primary degeneration" of the large Betz cells and a hyaline change in the walls of the blood-vessels in the cortex. Pentschew [27] confirmed these findings in his series, but was emphatic that they should not be considered specific.

There is some evidence that formation of excessive quantities of lipochrome is a disorder of cell metabolism. It is possible that in all these cases there is an exaggeration of the normal process of formation of lipochrome, which Marinesco [21] and Bertrand [2] have shown to be derived from the disintegration of the mitochondria; accumulation of the lipochrome in neuroglia and microglia may be the means by which transport of the excess of lipochrome is effected.

The chromatolytic changes which we observed in the nerve cells of the cerebral cortex, particularly in the Betz cells, are undoubtedly the same that Meyer [23], Cole [3], Mott [24], and other writers have described and to which Meyer gave the name "central neuritis." Meyer pointed out that these changes occur in the large pyramidal cells of the motor cortex in a high proportion of all cases of insanity, and that they are not peculiar to the syndrome of Korsakoff. Pearson [26], in a recent review of the whole subject of central neuritis, stated that he found the condition present in thirty-one brains out of a thousand examined consecutively. He observed chromatolysis only in the large and medium sized pyramidal cells of the motor cortex; it did not affect the prefrontal region or the smaller pyramidal cells as it did in our cases. The condition was present in many diseases other than diseases of the nervous system. Although in Pearson's series there were six cases in which

alcohol was a toxic factor, in most of the other twenty-five it could be definitely excluded. Pellagra was the only disease in which chromatolysis of the Betz cells was found in every case. Pearson came to the conclusion that the changes in the nerve cells are due to a disturbance of cellular metabolism in which a toxin acting directly or indirectly on the nerve cells prevents the nucleus from extracting nutritive material from the tissue juices. The cell therefore exists on the cell chromatin; the nucleus migrates to the axon hillock in order that the part of the cell which transmits the impulses shall be preserved as long as possible. If the toxin acts for long enough the nucleus ceases to function and the cell dies. These results of metabolic disorder will produce the appearance of the cells seen in "central neuritis," a term which Pearson rightly regards as misleading, since there is no change in the axon; the condition is not, therefore, an "axonal reaction." Pearson suggested the term "primary cytolytic degeneration" for the process, a term which certainly conveys the true impression that the process obtains in the cell itself and is not consequent upon an extracellular lesion of the neurone.

We are unable to confirm the observations of Marinesco [22] and Simchowitz [29], who found senile plaques in the cerebral cortex of patients who had had the Korsakoff syndrome. Marinesco's patient was aged 45, an age at which senile plaques do not occur except in advanced dementia. But Simchowitz's patient was aged 71, and she presented signs of dementia in addition to the psychosis associated with Korsakoff's syndrome, so that it is difficult to be sure that the plaques did not owe their existence to the presence of the condition of senile dementia.

We have already referred to our inability to demonstrate any tract degenerations in the spinal cord, even in the most long-standing of our cases. We can account for this absence of degeneration which so many others have observed only by postulating the selective action of the toxin in our particular cases.

From the histo-pathological examinations we have carried out we have evidence that in Korsakoff's syndrome certain changes in the nerve cells of the cerebral cortex occur in addition to the changes in the peripheral nerves which are those of a parenchymatous neuritis. The changes we found in the nerve cells were degenerative. They consisted in the deposition of the normal lipochrome pigment of the nerve cells in an excessive amount and in abnormal situations, such as the neuroglial and microglial cells, and around blood-vessels; and acute chromatolysis of the cortical nerve cells, especially of the Betz cells and of the larger

pyramidal cells in the frontal region. Complete disintegration of nerve cells was rare, even in cases of long standing. Inflammatory changes were absent and the fibre tracts of the brain and spinal cord were intact. The chromatolytic changes in the nerve cells are not specific for Korsakoff's syndrome. As we have already pointed out, these changes may occur in many toxic states.

But except that we did not observe hyaline degeneration of the cortical blood-vessels the changes in the cortex which we have demonstrated in cases of Korsakoff's syndrome correspond exactly to those described in the cortex of patients dying from pellagra; this is evidence that these changes are specific neither for pellagra nor for Korsakoff's syndrome. Whilst it is obviously impossible to assign a common cause to the two conditions (which have however certain clinical features in common, in that in both a peripheral neuritis is accompanied by a psychosis), it is possible that a common factor may be present in the two conditions. This factor may be a "deficiency" which permits a toxin to exert its effects on the highly specialized nerve cells of the cortex.

Summary.

(1) The ætiology of Korsakoff's syndrome and the criteria of nomenclature have been discussed.

(2) Five cases of Korsakoff's syndrome associated with alcoholism have been examined pathologically and the lesions found in the central nervous system have been described.

(3) The constant findings in the cerebral cortex were deposition of excessive amounts of lipochrome in all the nerve cells, in the neuroglial and microglial cells, and around the blood-vessels in the prefrontal and motor cortex, with acute chromatolytic changes in the larger nerve cells in these areas, especially in the Betz cells.

(4) The nature of these changes in the nerve cells has been discussed in relation to the question of a specific lesion in Korsakoff's syndrome.

(5) The view is expressed that the chromatolytic changes in the nerve cells is analogous to the appearances described by Meyer as "central neuritis."

(6) The similarity of the histo-pathological appearances between our cases of Korsakoff's syndrome and cases of pellagra has been remarked; both disorders show an enormous deposition of lipochrome in the cortical nerve cells, neuroglia and microglia at an age when normally lipochrome is present only in the nerve cells and in minute amounts, and also the central chromatolysis of nerve cells to which reference has already been made.

(7) The possibility is tentatively suggested that a common factor may operate in Korsakoff's syndrome and in pellagra, or that in these conditions there may be a deficiency in an essential factor, lack of which permits toxins to attack and damage the highly specialized nerve cells of the cerebral cortex.

It is a pleasure for us to acknowledge the kindness of Prof. Fraser, Dr. Riddoch, and Dr. W. Gordon Sears in permitting us to quote cases which were under their care.

Both of us carried out this work during the tenure of part-time grants from the Medical Research Council, for which we desire to express our thanks.

Finally we wish to thank Dr. J. Godwin Greenfield for the interest he has shown in our work and for kindly supplying the photomicrographs.

BIBLIOGRAPHY.

[1] Ballet, C., and Faure, M. *Presse Méd.*, 1898, **6**, 317.
[2] Bertrand, I., and Hadzigeorgiou, G. *Ann. de Méd.*, 1928, **24**, 119.
[3] Cole, S. J. *Brain*, 1902, **25**, 326.
[4] Dupouy, R., and Courtois, A. *L'Encéphale*, 1930, **25**, 284.
[5] Ely, F. A. *Journ. Nerv. and Ment. Dis.*, 1922, **58**, 115.
[6] Gamper, E. *Deutsch. Zeitschr. f. Nervenheilk.*, 1928, **102**, 122.
[7] Goldflam. *Ibid.*, 1923, **75**, 158.
[8] Greenfield, J. Godwin, and Holmes, Gordon. *Brain*, 1925, **48**, 183.
[9] Gudden. Quoted by Mott.
[10] Hall, A. J. *Brit. Med. Journ.*, 1929, **1**, 1025.
[11] Hösslin, R. von. *Arch. f. Psychiatr.*, 1905, **40**, 445.
[12] Hurst, E. Weston. *Brain*, 1925, **48**, 1.
[13] Korsakoff, S. *Zeitschr. f. Psychiatr.*, 1890, **46**, 475.
[14] *Idem. Arch. f. Psychiatr.*, 1890, **21**, 669.
[15] Korsakoff, S., and Serbski, W. *Ibid.*, 1892, **23**, 112.
[16] Kozowsky. *Ibid.*, 1912, **49**, 204, 556, 873.
[17] Ledoux, E. *Presse Méd.*, 1919, **37**, 516.
[18] Marcus, H. *Svenska Läk. Handl.*, 1926, **51**, 159.
[19] *Idem. Ibid.*, 1926, **52**, 28.
[20] *Idem. Ibid.*, 1927, **53**, 169.
[21] Marinesco, G. *Journ. Psychol. Neurol.*, 1930, **41**, 1.
[22] *Idem. L'Encéphale*, 1928, **23**, 697.
[23] Meyer, A. *Brain*, 1901, **24**, 47.
[24] Mott, F. W. *Brit. Med. Journ.*, 1910, **2**, 1403.
[25] Mourreyre, A. *Thèse de Paris*, 1899. Quoted by Serbski.
[26] Pearson, G. H. J. *Arch. Neurol. and Psychiatr.*, 1928, **20**, 366.
[27] Pentschew, A. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1928, **118**, 17.
[28] Serbski, W. *Arbeit. a. d. Neurol. Inst. Wien*, 1907, **15**, 351.
[29] Simchowicz, T. *Rev. Neurol.*, 1924, **1**, 221.
[30] Turner, J. *Journ. Ment. Sci.*, 1903, **49**, 673.
[31] *Idem. Brain*, 1903, **26**, 27.
[32] Weill, B., and Layain, F., *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, 1927, **51**, 145.
[33] Winkelman, N. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1926, **102**, 38.

EPILEPSY AND GUNSHOT WOUNDS OF THE HEAD.

BY W. E. STEVENSON.

(From the Ministry of Pensions Hospital, Maghull, Liverpool.)

THE frequency of occurrence of epilepsy after gunshot wounds of the head of all degrees of severity cannot be stated with accuracy, as statistics provided by medical observers are fallacious in that, for the most part, only those cases in need of treatment come under review.

Sargent [1] states that epilepsy had developed in 800 out of 18,000 cases of head wounds, that is, 4½ per cent. in 1920. At a later date, Bathe Rawling [2] traced 425 cases of head wound among whom 25 per cent. had developed "fits."

Wagstaffe [3] considers that fits are more common in proportion to the severity of the wound and where an organic lesion is present. Analysing 377 cases he found that the incidence of fits in the whole series, including concussion and fractured base without gunshot wound, was 10 per cent. whereas the incidence among those with penetrating wounds of the dura was 18 per cent. W. A. Turner [4] points out the important effect upon the estimate of the recognition of *petit mal* and epileptic equivalents which are so easily overlooked.

It was thought that inquiry at the present time would be likely to show a still higher percentage of traumatic epilepsy subsequent to gunshot wounds of the head, owing partly to the late development of epilepsy in a certain number of cases, and partly to the inclusion now of many cases of minor epilepsy not previously recognized as such. This, however, does not seem to be the case. A general survey of the official documents at the Ministry of Pensions in 17,300 cases of head wounds, the great majority of which are, of course, non-penetrating wounds, shows that epilepsy has been recorded as a second disability in only 270 cases. To these must be added head wounds with fits—not specifically diagnosed as epilepsy—and cases, fully pensioned, in which no claim for an additional disability has been made. Sargent's 800 cases probably include cases in which fits occurred at the time of being wounded, but in which an established and permanent epilepsy did not ensue. Allowing for these sources of error, it is probable that the percentage given by Sargent is still a fairly correct estimate. The

incidence of epilepsy in severe and penetrating head wounds must of course be much higher, but exact figures are not available.

It was at one time generally held that traumatic epilepsy develops within a few months of injury, and that a direct connection between injury of the head and subsequent "fits" could not be assumed unless the intervening period was comparatively short. In the majority of cases, especially of superficial wounds, this is no doubt true, but many authentic cases of epilepsy undoubtedly due to, but supervening years after, trauma of the head have been recorded. The mechanism operating in the late development of traumatic epilepsy is probably, as Sargent has suggested, the formation of adhesions, scar tissue and resultant drag. Foerster and Penfield [5] deal with the question of the scar traction on and in the brain in the development of traumatic epilepsy. These changes not only relate to the scar but also produce a marked dilatation and displacement of the ventricle in association with hydrocephalus. They consider this dilatation and displacement of the ventricle as due to scar traction which passes from the scar deeply through the scar-changed brain to the ventricle.

In Wagstaffe's series, the longest interval was seven and a half years. In the series upon which the present article is based, there are eleven cases in which ten years or more intervened between the trauma and the onset of definite epilepsy. The longest interval is fourteen years. It appears probable, however, that the majority of these cases belong to the group of unrecognized epileptics, and it must be very rare for epilepsy to develop a long time after the inducing trauma without warning such as vertigo, paroxysmal headache, short periods of "absent-mindedness," &c.

In most of the cases now under consideration, during the interval there had been frequent attacks of vertigo, and this, as is pointed out later, must be looked upon as probably an epileptic symptom. Nevertheless there are cases in which vertigo persists without the development of epilepsy, and it is a question whether the diagnosis of epilepsy on the presence of vertigo alone is justified. On the other hand, some few cases may develop epilepsy after a long period during which there is in fact no premonitory vertigo.

In Case 12 of this series, careful inquiry failed to elicit a history of vertigo or any other warning symptom. The wound was sustained in August, 1916, there was temporary hemiparesis which soon cleared up, and the patient was entirely free from symptoms till July, 1930, when he had a fit while at work, and he has since had two more. In Case 39—

wounded in 1916—the vertigo had been very infrequent and slight, and would not have demanded attention had not two fits occurred in 1929. In passing, it may be noted that in both these cases there was an intracranial foreign body. In Case 19, wounded in 1914, vertigo commenced nine years after the wound and the first actual fit occurred in 1926. He is now the subject of frequent major fits.

During the past twelve months, 84 cases of old gunshot wounds of the head have been treated in this hospital, and observation has been specially directed to the occurrence of epilepsy and mental deterioration, and the inter-relation between these two conditions. All the cases have had definite trauma of the head, but the degree varies within wide limits. They are therefore divided into two main groups: (1) Those showing definite evidence by palpation, or by X-ray, of severe trauma, e.g., gap in bone, metallic foreign bodies or fragments of bone in the cranial cavity. These comprise 54 cases. (2) Those with a definite history of gunshot wound of the head, but now showing no gross structural change resulting from this. These comprise 30 cases.

Of the 54 cases of penetrating wounds, 40 were subject to major epilepsy, or major and minor epilepsy combined, 3 had attacks of *petit mal* only; in 1 case there were Jacksonian attacks only, in 5 vertigo only, and in 5 cases the attacks consisted of emotional outbursts only and are described as "functional."

Of 30 superficial wounds of the head, 7 had major epilepsy, 5 had only *petit mal*, 4 suffered from vertigo only, 7 had only hysterical attacks, 1 case had Jacksonian fits confined to the right leg, and 6 cases were not diagnosed owing to absence of fits while in hospital, and the doubtful nature of the other evidence submitted.

Of the 84 cases under consideration, therefore, 57 were definitely epileptic (including 2 cases of Jacksonian epilepsy), 9 had vertiginous attacks which were probably closely related to *petit mal*, 12 had emotional outbursts which may be looked upon in some cases as hysterical, but in others were epileptic equivalents, and 6 cases were not diagnosed.

Vertigo.—The persistence of vertigo in gunshot wound of the head is of great importance in prognosis. Nearly all cases of delayed traumatic epilepsy are characterized by frequent attacks of vertigo during the years intervening between the gunshot wound and the onset of epilepsy. Such vertigo seems to be closely allied to minor epilepsy, and tends to become more severe as time goes on, until it may be accompanied by transient loss of consciousness. In some cases of vertigo, major epilepsy

does not ensue, but the vertiginous attacks assume an epileptic type. They are accompanied or followed by slight mental confusion and symptoms of vaso-motor disturbance, pallor, flushing, sweating, &c. Chartier [6] has described such attacks under the name of "Reflex Vertigo."

"*Functional*" *attacks.*—These are characterized by loss of emotional control. There is no loss of consciousness, no true vertigo, and but little confusion. They tend, usually, to be longer in duration than attacks of vertigo and *petit mal*, but this is not always the case. In some cases there is irregular jactitation, in others resistiveness or apparently purposeless violence.

Epileptic equivalents.—Epileptic equivalents are met with in traumatic, though probably not so frequently, as in idiopathic epilepsy. In several cases of this series emotional outbursts replaced, or alternated with, major epileptic fits. Wandering and automatism associated with *petit mal* occurred in three cases. Two cases of so-called procursive epilepsy were noted, in which sometimes before a fit the patient would run about in an automatic or confused way.

In the absence of major attacks, equivalents present difficulties of diagnosis. They have to be distinguished from hysterical manifestations; for equivalents, dreamy states, periodic depression, are symptoms of a permanent mental change. The question arises whether the occurrence of equivalents points to "predisposition." Feuchtwanger, quoted by Peritz, concludes that, when a large group of cases is considered, epilepsy following brain damage shows in its clinical picture all the symptoms which are also seen in genuine epilepsy; attacks, aura, giddy states, periodic depression, minor attacks, absences, dreamy states, confusional states, dementia, alterations of character and disposition. In the individual case there is no symptom which, from its manifestation alone—e.g., equivalent, alteration of personality, &c.—allows of conclusions as to an "epileptic predisposition" or "latent epilepsy."

The occurrence of equivalents and mental changes observed in the group of cases on which the present article is based is in conformity with the conclusions quoted above.

As regards skull injury in which brain injury is uncertain, though equivalents in themselves cannot be regarded as argument in the sense of a predisposed genuine epilepsy as against a traumatic, occurring in conjunction with other factors—e.g., psychopathic heredity, alcoholism, pretraumatic instability, &c.—they would support the argument of epileptic predisposition.

Jacksonian epilepsy.—Jacksonian epilepsy is now rarely met with among pensioners with head wounds, although in a few cases the fits tend to be localized or more marked on one side than the other. In some cases there is a history of Jacksonian epilepsy occurring shortly after the wound, ceasing for a time and being succeeded, perhaps years later, by generalized major epilepsy. A history of Jacksonian epilepsy is not, however, to be relied on, as the term, "Jacksonian epilepsy," appears to have been used often loosely as synonymous with traumatic epilepsy.

Adie and Wagstaffe [8] state that cases with localized fits at the time of the wound are not more liable than others to develop subsequent traumatic epilepsy.

Wagstaffe appears to have revised this opinion, for, writing at a later date, he states that traumatic epilepsy appears to be much more common in those cases which developed transient Jacksonian fits within a few days of the injury.

Among this series there were only two cases of Jacksonian epilepsy. In both cases the wound was situated exactly over the upper end of the left central sulcus. The seizures were limited to the right leg, there was not complete loss of consciousness, and in one case there was wasting of the leg.

Mental deterioration.—In relation to mental deterioration, two factors were investigated: the type and frequency of the fits, and the site and severity of the head wound. Of these two factors, the first appears to be the more important, although the latter is not without its effect. Of severe head wounds, 40 out of 54 showed some degree of mental deterioration, i.e., about 75 per cent. Of those with less severe wounds, 13 out of 30 showed some deterioration, i.e., about 43 per cent. Of 17 cases of severe trauma with frequent fits, all were mentally deteriorated in some degree, i.e., 100 per cent. Of 37 cases of severe trauma with infrequent fits, or functional or vertiginous attacks only, 23 were deteriorated, i.e., 62 per cent.

In Table I these figures are compared with 108 cases of idiopathic epilepsy in whom mental deterioration was present in 94 per cent. of those with frequent fits, and in 47 per cent. of those with infrequent fits. Superficial wounds of the head show less deterioration than idiopathic epilepsy, because they include cases which are not in fact epileptic.

Site of wound.—(1) Anterior to, and not involving, the motor cortex. In twelve out of fifty-four cases of severe gunshot wound, the damage appeared to be limited to the anterior frontal areas.

The characteristics of trauma limited to the prefrontal areas are infrequency of fits, absence of aura, impairment of memory with a peculiar alteration of emotional tone, and in many cases a long latent period between the trauma and the onset of epilepsy. The average period between the infliction of trauma and the onset of epilepsy in these twelve cases is over six years; the longest period is fourteen years. This latent period, however, in nearly every case is characterized by vertigo and frequent headache.

TABLE I.—INCIDENCE OF MENTAL DETERIORATION IN IDIOPATHIC AND TRAUMATIC EPILEPSY.

		No impairment	Emotionally unstable without intellectual deterioration	Slightly deteriorated	Moderately deteriorated	Severe deterioration	Deterioration
Frequent fits (more than 24 major attacks a year or 12 minor monthly)	Consequent upon severe GSW head	—	—	7	5	5	100 %
	Subsequent to superficial GSW head	—	—	1	—	—	—
	Idiopathic ..	1	3	21	25	18	94 %
Infrequent fits including also vertigo only or "functional" attacks only	Consequent upon severe GSW head	10	4	11	11	1	62 %
	Subsequent to superficial GSW head	10	7	8	4	—	41 %
	Idiopathic ..	12	7	12	8	1	52 %

When the trauma is strictly limited to the anterior frontal area there is complete absence of aura, and, when the fits are diurnal, this lack of warning involves danger from sudden falls. The wearing of a suitable head-shield is therefore often necessary. Where an aura exists with a frontal injury, full investigation will always reveal an additional area of trauma. For example, in Cases 46 and 47, though the main site of trauma was at the frontal pole, a gustatory aura was complained of. Full investigation left little doubt that the temporal lobe was also damaged. Where the damage tends to encroach on the motor area of the cortex, as is to be expected, a motor aura is often found. This may be very limited, e.g., a rotation and fixation of the head, and serve as a quite inadequate warning to the patient.

When fits occur in purely frontal injuries they are comparatively infrequent, usually of major type, and well spaced, that is to say, the intervals between fits are long, two or three months or more, and there

is little or no tendency for the fits to group. Status epilepticus, in my experience, is very rare in traumatic epilepsy where the injury is strictly limited to the anterior frontal region.

Of these 12 cases, one had had only 3 fits in all; of the other 11 cases, the average number of fits per year was 14. In 7 cases the fits were of major type only, in 3 cases *petit mal* and *grand mal* both occurred, and in 2 cases there were only attacks of vertigo and possibly *petit mal*.

An alteration of emotional tone peculiar to injury of the frontal region was observed. This consists in emotional dulling, with a loss of interests in general, combined with a certain peevishness and irritability when in any way restricted or interfered with. There is, as it were, a loss of capacity for normal enjoyment and pleasure, and at the same time a centring on self, leading to irritability and impatience with others. The memory is usually more or less impaired, but intellectual enfeeblement does not proceed so rapidly or so far as in those cases of traumatic epilepsy in which the fits are more frequent, and especially in those in which the fits tend to group. In two cases of this sub-group there was no apparent defect of memory or of emotional control; one of these had only three major fits in all, and the other had only infrequent *petit mal*.

Motor or sensory defects do not occur when the injury is limited to the prefrontal area, but impairment of stereognostic sense was found in two cases, though the injury seemed to be definitely limited to the area under discussion.

(2) Trauma involving the motor cortex. In twenty-three of the fifty-four cases of severe trauma, the motor cortex was involved. As would be expected, a motor aura is usual in such cases, but this is often of such short duration as to afford no adequate warning. The interval between the wound and the onset of epilepsy is noticeably shorter than in trauma of the other cerebral areas. Most of these cases developed epilepsy within a few months of being wounded, and, where in a few cases there is an apparently long latent period, inquiry generally produced a history of vertigo, mental blanks, &c.

In most cases of traumatic epilepsy, when the motor cortex is involved the fits are of major type, tend to become more frequent with the passage of time, and tend to group, so that status epilepticus is not uncommon. Of the 23 cases, 12 were the subject of very frequent major and minor attacks, 4 had major epileptic fits about once a month, 2 had very infrequent major fits and occasional epileptic equivalents, 3 had very rare major fits with frequent vertigo or *petit mal;* one case suffered from occasional vertigo, but had never had a definite

epileptic attack, and one case had functional attacks (emotional outbursts) only.

Mental deterioration is marked in this group, and not infrequently psychoses, temporary or permanent, develop. Most often the psychosis takes the form of a more or less transient mania and confusion, but stupor and hallucinational and delusional forms have been observed. Where damage of the anterior frontal areas is added to that of the motor cortex, there is a slowly progressive dementia, emotional dulling and apathy, gradually replacing emotional instability and tendency to mania.

Epileptic equivalents were noted in two cases of this group. In one case (No. 32), wandering in a state of fugue occurred occasionally in the intervals between major epileptic fits. In the other case (No. 28), outbursts of uncontrollable weeping or emotional excitement have to a large extent replaced fits formerly of generalized major type with a motor aura of the left hand and face.

Various degrees of paresis, varying from complete cortical hemiplegia to subjective sensations of weakness, are found in this group. These tend to improve, but it is seldom that some residual sign of lesion of the motor path, such as a Babinski reflex, cannot be found.

(3) Injuries posterior to the motor cortex. In ten cases in which the trauma was entirely posterior to the motor cortex, the most noticeable feature was the infrequency of fits. In three of these cases fits have now ceased, and are represented only by periodic unreasonable and uncontrollable emotional outbursts. In four other cases there have been only six major fits or less all told. Aura was absent except in two cases (Nos. 36 and 40). In one of these there was a visual aura, consisting of flashes of light and hemianopsia for a quarter of an hour before the fit, and not infrequently this aura occurred without a fit ensuing. Byrom Bramwell [8] has described a similar condition occurring in tumour of the occipital lobe under the picturesque name of Visual Jacksonian attacks. In the other case there was sometimes a visual, sometimes an auditory aura. Three of this group showed no mental deterioration, and in the others the degree of deterioration was slight. In one case (No. 45), the cerebellum was peppered with numerous small metallic foreign bodies, but none of the classical signs of cerebellar lesion was present.

(4) Injuries involving the temporal lobe. In six cases the main trauma appeared to have fallen on the temporal lobe, usually in association with damage to the frontal or the parietal cortex. In two

of these cases the fits were all of minor type, but were associated with automatism and epileptic equivalents, and in four cases both major and minor fits occurred, were rather frequent and tended to group. In three cases, fits associated with a gustatory aura were noticeably prone to occur at meal times.

Four out of these six cases showed marked mental deterioration. The other two cases, though not deteriorated, were liable to confusion and automatism after fits.

One case (No. 47) developed *petit mal* with an aura of nausea eleven years after being wounded. During the "latent period," however, he had had periodic attacks of unexplained nausea and vomiting. It is possible that this nausea and vomiting were actually an aura without subsequent fit, or there may have been *petit mal* of such short duration as to escape notice. In this case both frontal lobes had been damaged and there was a foreign body in the left temporal pole.

(5) In three cases the bullet had entered anteriorly and had been extracted from the posterior part of the brain, so that it was not possible to localize the main seat of trauma. In all these cases the mental deterioration was marked. In two the fits were frequent, and in the third, though actual fits were few, there was frequent severe vertigo.

Superficial wounds.—It is admitted that the degree of cerebral injury cannot be estimated by the extent of the wound and injury of the skull. Nevertheless my experience of these cases leads me to believe that "epileptic predisposition," or "nervous instability" plays a larger part in the production of "fits" in those with superficial wounds than in those with deep and permanent trauma. Cases of epilepsy associated with painful superficial scars have been described under the term "reflex epilepsy," and Oppenheim [9] has called attention in particular to this cause of epilepsy following cranial injuries. All cases of this kind which have come under my observation have proved on investigation to be "functional," not epileptic. The stimulation of such a scar by handling serves to revive a painful effect associated with the original trauma and induces an emotional outburst sometimes accompanied by some degree of dissociation.

In the great majority of scalp wounds, the fits, whether "functional" or epileptic, are the result of shock, fear, or other emotion reacting upon an unstable nervous system, and are not due to structural damage or direct irritation by cicatrices, adherent dura, &c. Such fits supervene within a short period of the injury, but a permanent epileptic or "epileptoid" condition may be established.

TABLE II.—FREQUENCY OF FITS IN RELATION TO SITE OF INJURY.

	Frequent	Infrequent	Minor only	Vertigo only	Functional	Total
Frontal—not involving motor cortex	3	8	—	1	—	12
involving motor cortex	12	9	—	1	1	23
Posterior to motor cortex	3	4	—	—	3	10
Involving temporal lobe	4	—	2	—	—	6
Traversing wounds	2	—	—	1	—	3

Of the thirteen cases in which a definite diagnosis of epilepsy could be made, one has Jacksonian attacks limited to the right leg, and accompanied by transitory confusion. These attacks commenced nine years after being wounded, though there had been complaint during the interval of weakness and numbness or pain in the leg. The scar is situated over the upper end of the left central sulcus, but X-rays show no evidence of damage to the bone. In another case there was a "latent period" of seven years, which, except for headache, was devoid of symptoms. Definite minor epilepsy was observed during this patient's residence in hospital, and he was stated to have had infrequent major fits at home. In two cases of superficial temporo-frontal injury, five years elapsed from the date of the wound to the onset of epilepsy. In eight cases epilepsy commenced within a few months of injury. In other cases there were claims for epilepsy after long latent periods, but a positive diagnosis was not possible owing to the absence of fits, or even of vertigo, while under observation in hospital.

Seven of this group were considered to be definitely hysteric, not epileptic.

CONCLUSIONS.

The term "traumatic epilepsy" should be limited to cases of epilepsy resulting from injury to the brain or its membranes. The term "Jacksonian epilepsy" should be applied only to localized fits of cortical origin.

Traumatic epilepsy may develop as late as ten years or more after severe injury of the head, but usually there has been in the interval vertigo, paroxysmal headache, or other premonitory symptoms. Epilepsy following superficial wounds of the head is most often psychogenetic in origin. The fits in such cases are the result of shock, fear, or other emotion reacting upon an unstable nervous system, and are not due to structural damage or direct irritation by cicatrices, &c. Such epilepsy supervenes within a short period of the injury.

The fits in traumatic epilepsy are, in most cases, clinically the same

as in idiopathic epilepsy. Both major and minor attacks occur. In severe gunshot wound of the head there are, however, certain variations in the type of subsequent epilepsy. These variations, though not absolute, are sufficient to form a basis for differentiation, and an aid in diagnosis. They depend upon whether the trauma involves the motor cortex, or whether it is mainly anterior or posterior thereto. Epilepsies following lesions of the temporal lobe have also their local signs. These differences are mainly observed in penetrating wounds, but may serve, in superficial lesions, to distinguish a true traumatic epilepsy from an epiplepsy of psychogenetic origin. When there has been a long latent period, with complete freedom from symptoms, more recent possible cause of epilepsy must be excluded before the epilepsy can be considered of traumatic origin.

Vertigo is more common in traumatic than in idiopathic epilepsy, and in some cases may be the only epileptiform symptom. In other cases it may precede the onset of definite epileptic attacks by many years.

Mental deterioration is more rapid in traumatic than in idiopathic epilepsy. It is related mainly to the frequency of the fits, but, when fits are infrequent, deterioration is more rapid and marked in severe wounds of the head than in idiopathic epilepsy with a similar frequency of fits.

I desire to express my thanks to the Director General of Medical Services of the Ministry of Pensions for permission to publish this article.

REFERENCES.

[1] Sargent. *Brain*, 1921, **44**, 312.
[2] Rawling. *Brit. Journ. Surg.*, 1922, **10**, 93.
[3] Wagstaffe. *Lancet*, 1928, **11**, 861.
[4] Turner. *Journ. Neur. and Psychopath.*, 1923, **12**, 310.
[5] Foerster und Penfield. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1930, **125**, 475-572.
[6] Chartier. "Neurologie de Guerre."
[7] Adie and Wagstaffe. Report to the Medical Research Committee, 1918.
[8] Byrom Bramwell. "System of Medicine," Allbutt and Rolleston, viii, 276.
[9] Oppenheim. "Diseases of the Nervous System," English Trans. Ed., p. 890.

FACTORS DETERMINING THE DIFFERENTIATION OF THE CEREBRAL CORTEX IN SEA-LIVING MAMMALS (THE CETACEA). A STUDY OF THE BRAIN OF THE PORPOISE, TURSIOPS TRUNCATUS.

BY ORTHELLO R. LANGWORTHY,

Sub-department of Neurology, The Johns Hopkins University.

COMPARATIVE neurological studies of the common vertebrates have furnished illuminating data concerning the phylogenetic development of the cerebral cortex. Into the anterior portion of the neural axis, which was at first dominated by the olfactory nerve, other types of sensory impulses have penetrated. Perhaps the first to reach this region were trigeminal, carrying impulses from the snout and the sinus hairs; optic, acoustic and fibres from cutaneous and deep structures of the body eventually reached the cortex and developed end-stations there. Around these projection areas other portions of the cortex were differentiated for the correlation of these stimuli. This neocortex developed in the dorsal portion of the old olfactory pallium, and with its further growth the older olfactory cortex was pushed to the mesial and lateral surfaces of the hemispheres.

If the story of the phylogenetic development of the central nervous system is followed, it will be realized that there have been other attempts to develop dominant correlation centres in the cephalic portions of the neural axis. In lower vertebrates, perhaps reaching their highest relative development in birds, the optic end-stations in the roof of the mid-brain were of great importance. The cells became arranged in a laminated pattern, similar to that developed in the cerebral and cerebellar cortices. Other types of sensory fibres were attracted into this region, in particular the acoustic fibres. But this correlation centre did not flourish and has undergone regression in mammals. This is perhaps due to the fact that there is tendency for dominance in the most cephalic portion of the neural axis. Dr. Adolf Meyer has called the roof of the mid-brain an archæological museum.

The cerebral cortex, however, has undergone extremely rapid growth and differentiation in Primates, culminating in the fore-brain cortex of man; again, comparative neurologists have speculated concerning the contributing factors. Many investigators believe that, in this case, influences from the visual apparatus played a dominant part. With the

regression in size of the snout and the movement of the eyes to the front of the head, binocular stereoscopic vision became possible. This gave a certain depth and perspective to objects in the environment. With the acquisition of this better perspective by the animal the fore-legs began to be utilized for seizing food and climbing in the trees, and were more and more freed from their function as locomotor props. The cerebral cortex, under the influence of afferent impulses from the eyes, thus came, in time, to control the finer co-ordinated movements of the hands.

A sharp contrast to this story is the history of the evolution of the cerebral cortex of the Cetacea. These mammals present an interesting history of adaptation. After they had reached a stage of development comparable to that of the Carnivora (cat and dog) they became adapted to a life in the water. This produced marked changes in all portions of the body, including the central nervous system. In the adjustment to an aquatic environment the hind-leg was lost, so that only minute vestigial remains are found within the body of the porpoise. The fore-leg, likewise, underwent a marked reduction, changing its conformation and becoming the flapper. The tail developed into a powerful muscular appendage, supplemented by the growth of caudal flukes, highly adapted to locomotion in the water. The skin has become thick, smooth and hairless, and has lost its sweat, as well as sebaceous, glands. The pinna of the ear has been lost and the external auditory meatus reduced. Furthermore, the eyes and the eyelids have undergone pronounced modifications. Many of these changes upon the surface have been brought about to further the ease of gliding through the water.

The author had the opportunity a few years ago of visiting a porpoise fishery off the coast of North Carolina with a group of workers interested in this unique animal. Six young adult males, each 8 ft. long and weighing about 800 lb., were caught upon a single morning. It had been hoped that certain physiological studies relative to the nervous system could be made at the fishery. For example, it was planned to stimulate the cerebral cortex with a faradic current and also to produce decerebrate preparations. These experiments were largely unsuccessful, due to technical difficulties. However, the brains were removed and carried to Baltimore for further study. Both macroscopic and microscopic examinations were made; through the kindness of Dr. Adolf Meyer several serial sets of sections were stained by the Weigert-Pal technique. A detailed report of the findings is published in another place. The drawings that illustrate this paper were made by Mr. James Didusch of the Carnegie Institution of Washington.

When the central nervous system of the porpoise is examined, it is found that the cerebral cortex is very large and well differentiated. The lateral surface of the brain is shown in fig. 1, and it is at once clear that the pattern of convolutions is even more complicated than that observed in man. Structural changes in the shape of the skull have had an effect on the conformation of the cranial cavity and of the brain. A marked foreshortening of the skull has occurred, brought about by telescoping of this structure, so that the frontal and occipital bones override the parietal bones, producing a cranial cavity which is deep and wide but relatively short antero-posteriorly. The

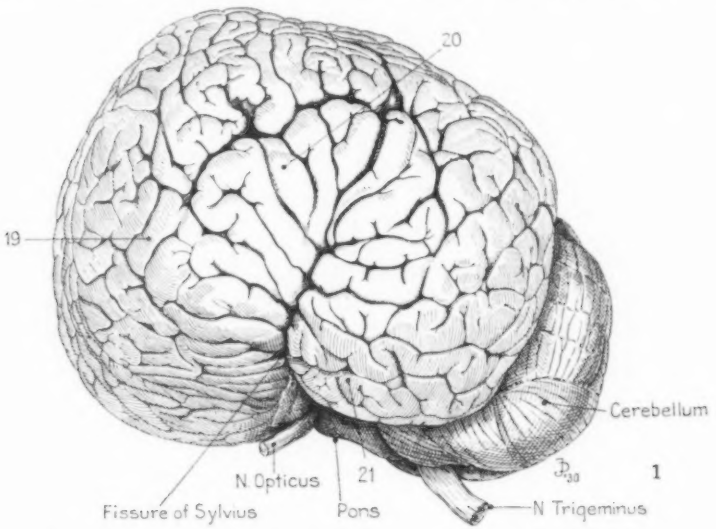


FIG. 1.—Drawing of lateral surface of the cerebral cortex of the porpoise.

blow-hole, a complex naso-pharyngeal structure adapted to the regulation of intake and escape of air, has developed anterior to the cranial vault. With the formation of the blow-hole mechanism, the nostrils have shifted to the dorsum of the head.

These changes are all mirrored in the brain, which is wide laterally and foreshortened antero-posteriorly. The frontal surface is flat, rising abruptly from its ventral to its dorsal surface. Since the skull has been flattened anteriorly to leave room for the blow-hole mechanism, considerable rotation of the fore-brain has occurred. This causes the fissure of Sylvius to extend in a vertical rather than a horizontal plane (fig. 1).

The occipital lobe is not large; the temporal lobe is a conspicuous portion of the cerebral cortex. Former investigators have suggested that the shape of the fore-brain was determined by the absence of olfactory nerves or nuclei; undoubtedly the mechanical factors just mentioned are much more important.

The fissure of Sylvius may be identified in fig. 1. A number of gyri radiate from this fissure. These are bounded laterally by a semi-lunar fissure, the supra-Sylvian fissure. A number of previous workers have studied the pattern of gyri and sulci in the cortex of the porpoise and have attempted to homologize them with those found in other

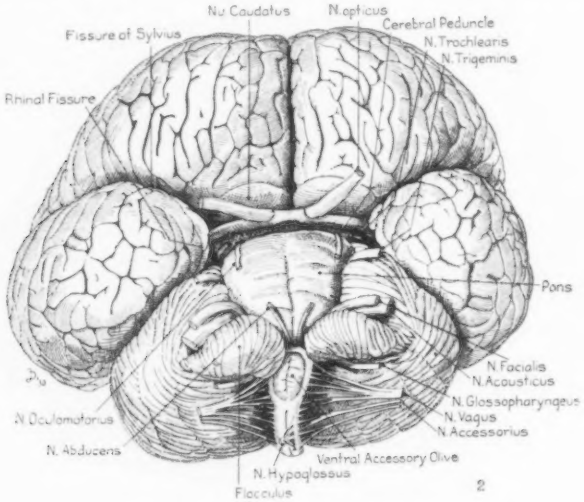


FIG. 2.—Ventral view of porpoise brain.

mammals, particularly carnivora. The present study endeavoured instead to determine the types of sensory fibres reaching the cerebral cortex and to localize the primary projection and correlation centres there.

The ventral surface of the porpoise brain is pictured in fig. 2. The caudate nuclei lie on the surface of the brain at the ventral edge of the frontal lobes. The rhinal fissure may be identified at the very tip of the temporal lobe. The great width of the fore-brain is evident from this drawing.

The cerebellum is very large (figs. 1 and 2) and consists of two large hemispheres with a small vermis squeezed between them. The con-

spicuous flocculus is characteristic of all water-living mammals. It is also evident that the connections of the cerebral with the cerebellar hemispheres are well developed inasmuch as the pons is so conspicuous.

This drawing of the ventral surface of the brain shows (fig. 2) the cranial nerves. No remnants of olfactory nerves or olfactory bulbs were found in any of the six brains examined. It is probable that all the optic fibres cross in the chiasma and reach the opposite thalamus. The oculomotor, trochlear and abducens nerves are not remarkable. The trigeminal nerve is well developed; the ophthalmic branch is greatly diminished in size, but the maxillary and mandibular are large. The facial nerve is particularly differentiated in that it innervates the complicated musculature of the blow-hole apparatus. The acoustic nerve is very large and it is the cochlear portion which shows the greatest development. The glossopharyngeal, vagus, accessory and hypoglossal nerves are not remarkable.

The present paper is concerned with the factors contributing to the great differentiation of the cerebral cortex in the porpoise; the gross and microscopic structure of the nervous system has been described at some length in another paper (Langworthy, 1931). Perhaps the first step is to determine the relative development of pathways carrying sensory impulses to the cerebrum.

The fore-brain is fundamentally an olfactory end-station, but no olfactory nerves or olfactory bulbs were present in the six porpoise brains examined. The olfactory correlation cells and tracts were either absent or greatly reduced in size. This was also found by Addison (1913) in studying the rhinencephalon of the dolphin (*Delphinus delphis*). The olfactory cortex at the base of the frontal lobe is absent in the porpoise and the head of the caudate nucleus projects on the ventral surface of the brain. The parolfactory area is represented and gives rise to the stria medullaris and stria semicircularis. All of these structures are of small size. The hippocampus is very diminutive, as is also the fornix which ends in a small group of cells, the mammillary body. From the mammillary body a tenuous tract goes to the anterior nucleus of the thalamus. The mammillary body cannot be distinguished macroscopically on the ventral surface of the brain. No tracts can be followed to the hippocampus major. The anterior commissure was not identified. The presence of the parolfactory area and hippocampus major, although diminished in size, suggests that they have other than olfactory connections. Edinger believed that the parolfactory area is

the centre for an oral or snout sense mediated largely by the trigeminal nerve. It is clear, therefore, that no olfactory nerve fibres enter the central nervous system of the porpoise and the olfactory nuclei in the fore-brain are greatly reduced in size.

Sections of the spinal cord were examined to localize pathways carrying afferent impulses from the cutaneous and deep structures of the body to the thalamus and cortex. The anterior horns of the gray matter are large and contain numerous motor cells arranged in groups or clusters. The posterior horns, on the other hand, are rather small. The ventral roots of the spinal cord appear to be larger and to contain many more fibres than the dorsal. The ventral tracts of the cord are differentiated out of all proportion to the lateral and dorsal tracts. It is probable that the anterior columns contain many short intersegmental fibres, correlating the activity of the musculature. The posterior columns are fairly large and may be divided, in the upper portion of the cord, into gracilis and cuneatus tracts. The fibres of the posterior columns end around the cells of the posterior column nuclei in the medulla; the medial lemnisci are fairly developed and may be followed to the thalamus. In this way impulses from the muscles must eventually be relayed to the cerebral cortex. In proportion to the bulk of the striated musculature and the delicate co-ordination of movements, this pathway carrying afferent impulses from the muscles to the cortex is small.

The skin of the porpoise is so thick that it is not adapted to the reception of delicate shades of stimuli. There are probably few and poorly differentiated cutaneous sensory nerve endings. The pain-temperature tract or spino-thalamic tract is very small.

The trigeminal nerve carries stimuli to the central nervous system from the region of the head. Again cutaneous sensation must be decreased in the porpoise, but the naso-pharynx probably contains numbers of sense organs. The sensory nuclei of the trigeminal in the medulla have all been identified but they are of relatively small size. Trigeminal stimuli have played little part in the development of the cerebral cortex.

The importance of the optic nerve in the differentiation and rapid growth of the cerebral cortex in higher mammals has already been emphasized. In the porpoise, however, the optic bulbs are placed so far laterally upon the head that binocular stereoscopic vision is impossible. Moreover, it has been clearly shown by one observer that, in the dolphin at least, all the optic fibres decussate in the midline so that

there are no arrangements in the central nervous system for anything more complicated than panoramic vision. The optic end-stations in the roof of the mid-brain and in the thalamus are small. Although optic fibres reach the cerebral cortex they can scarcely have played a prominent part in its unusual growth.

The optic nerve is indicated in fig. 1 and the chiasma in fig. 2. The optic colliculi in the roof of the mid-brain are much smaller than the acoustic (fig. 3). This proportion is reversed in other groups of mammals. Moreover, in fig. 3 the acoustic geniculates are large; the optic geniculates can scarcely be discerned and appear only as small swellings in the course of the optic tracts.

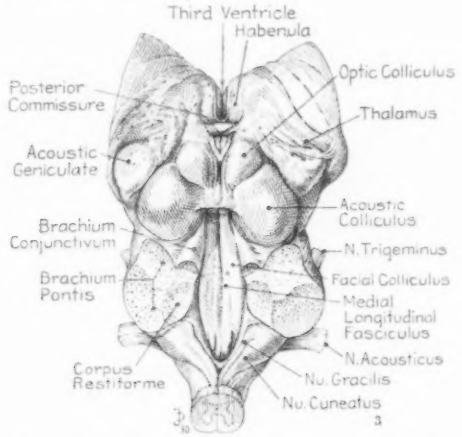


FIG. 3.—Dorsal surface of the brain-stem of the porpoise, to show particularly the acoustic colliculi and acoustic geniculates.

The acoustic nerve, on the other hand, is very large. Examination shows that it is the cochlear and not the vestibular portion that is of great size. The vestibular nerve compares favourably in size with the other sensory components already discussed; the cochlear nerve far surpasses them. Moreover, the acoustic connections in the brain are the conspicuous landmarks both on macroscopic and miscroscopic examination.

There is no evidence at the present time that the sense of hearing is particularly acute in the porpoise. It must be remembered in this connection that the acoustic apparatus had to be completely reorganized for use in a fluid media. It may be due to this functional adaptation that the cochlear mechanism has hypertrophied. It is remotely possible

that the cochlear portion of the nerve has taken over the function of controlling equilibrium in the porpoise.

The cochlear nerve is seen in fig. 2; the acoustic colliculi and geniculates in fig. 3. The acoustic colliculi lie further from the midline and are larger than the optic. They are connected across the midline by a commissure of fibres. There is another peculiarity of the acoustic geniculates in addition to their size, for, in the porpoise, they do not present a smooth surface but are thrown into folds and ridges. This demonstrates the marked expansion and development of this region; perhaps it represents an attempt to supply nutrition to a larger area, utilizing the blood supply already present. The marked unfolding of the cerebral and cerebellar hemispheres, characteristic of certain mammals, may be an adaptation to produce adequate vascularization.

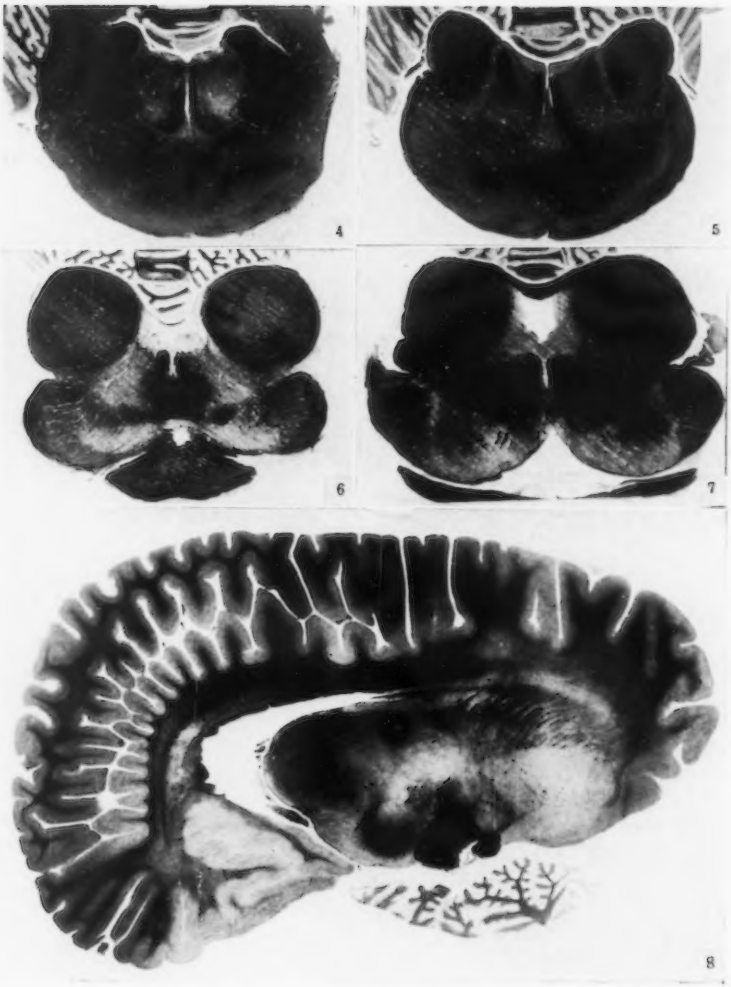
Photomicrographs of the brain demonstrate the acoustic connections. Fig. 9 shows a transverse section through the brain-stem at the level of the acoustic nerves. The great size of the cerebellum is also evident; the hemispheres are particularly well developed while the vermis is squeezed into the dorsal midline. The flocculi project beneath the ventral surface of the brain-stem. The contour of the dentate nuclei of the cerebellum is characteristic; in most mammals with large cerebellar hemispheres the dentate nuclei are markedly convoluted, while here they form an almost solid mass of cells.

Another transverse section through the cerebellum shows the acoustic lemnisci (fig. 10). These fibre tracts are associated on their mesial surfaces with a conspicuous mass of cells, the nuclei of the acoustic lemnisci which are white in the photomicrograph. The pons lies ventral to the acoustic tracts. The brachia conjunctiva, consisting largely of efferent fibres from the cerebellum, projects into the fourth ventricle.

The large size of the pons is shown more clearly in fig. 4. The two dark groups of fibres just ventral to the fourth ventricle form the brachia conjunctiva; the large fibre bundles which stain gray are the acoustic lemnisci. Fig. 5 represents a section slightly cephalic to fig. 4. The dorso-lateral bundles of fibres represent the caudal portion of the capsule of the acoustic colliculi, or the acoustic lemnisci just caudad to the colliculi. Mesially are the brachia conjunctiva, while the pontine nuclei and fibres form the ventral portion of the section.

The acoustic colliculi occupy over one-third of the transverse diameter of the brain-stem in fig. 6. They are almost circular and consist of a mass of nerve cells surrounded by a capsule of fibres. The section just

PLATE V.



Photomicrographs of sections of the porpoise brain stained by the Weigert-Pal method.

FIG. 4.—Transverse section of the brain stem. The large grey bundles of fibres at the lateral edges of the section are the acoustic lemnisci.

FIG. 5.—This section cuts the caudal edge of the acoustic colliculi and shows the acoustic lemnisci forming the caudal capsule of the colliculi.

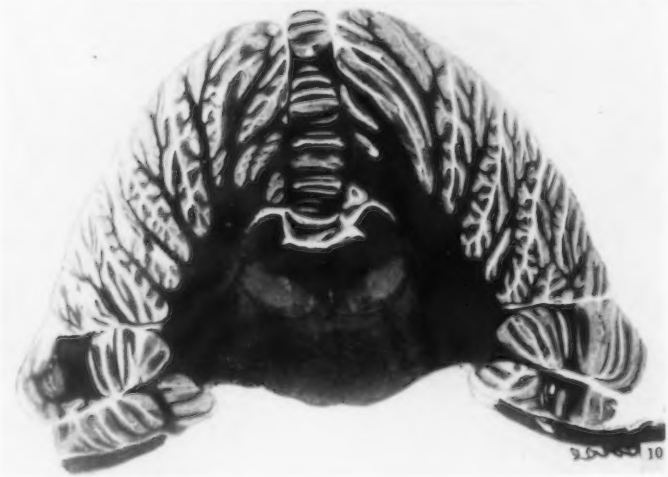
FIG. 6.—Transverse section through the acoustic colliculi.

FIG. 7.—The acoustic colliculi are connected by a group of commissural fibres which lie dorsal to the aqueduct of Sylvius.

FIG. 8.—The caudal prolongation of the thalamus resembles in its contour the optic pulvinar of other mammals. It contains many myelinated fibres. Study of the sections demonstrated that the acoustic fibres end in this region and it is acoustic rather than optic in its connections.

To illustrate paper by Orthello R. Langworthy.

9



10

FIG. 9.—Transverse section through the brain-stem at the level of the acoustic nerves. The cerebellar hemispheres and the flocculi are large; the vermis is compressed in the midline. The dentate nucleus of the cerebellum consists of an almost solid mass of cell.

FIG. 10.—The nuclei of the acoustic lemnisci are large and show as white masses just above the pons. The nucleus of the acoustic lemniscus lies ventro-lateral to the fibres.

To illustrate paper by Orthello R. Langworthy.

cuts the upper end of the pons; the cerebral peduncles project laterally. The pale areas just dorsal to the pons are the substantia nigra; the colour discrepancy is due, of course, to the staining of the section. Fibres of the brachia conjunctiva are crossing in the midline. Ventro-lateral to these fibres are the mesial lemnisci. Dorsal to the brachia conjunctiva the medial longitudinal fasciculi lie close to the midline.

The acoustic colliculi are connected by a group of commissural fibres, shown in fig. 7, above the aqueduct of Sylvius. A portion of the optic chiasma is ventral to the brain-stem. Of particular interest is the separation of the fibres in the cerebral peduncles in a number of tracts.

Fig. 8 is a photomicrograph of a sagittal section through the whole fore-brain, and shows first of all the complexity of the sulci and gyri. The inferior horn of the ventricle can be followed to the tip of the temporal lobe. At the ventral edge of the brain-stem there are three groups of nerve fibres; the one on the right is the optic tract, in the centre the cortico-efferent paths, and on the left acoustic fibres which end in the thalamus.

The corpus striatum may be seen dorsal to the optic tract; in this section the globus pallidus, caudate nucleus and the tail of the caudate nucleus at the dorsal edge of the brain-stem are visible. There is no great development of the putmen in the porpoise.

The caudal prolongation of the thalamus contains numbers of myelinated fibres. It has the contour of the optic pulvinar of mammals, but in reality it is a section of the large acoustic geniculate.

These few photomicrographs demonstrate that the acoustic nuclei and tracts in brain of the porpoise are all large and form the most conspicuous sensory cells and pathways in the brain-stem. The acoustic stimuli must have had the greatest influence on the differentiation of the cortex.

The stimulus of increased numbers of acoustic impulses entering the acoustic colliculi has had no marked effects upon their structure or differentiation. In land mammals the acoustic colliculi have a much more primitive structure than the optic. While the cells of the optic colliculi have a laminated appearance, the acoustic colliculi consist of a solid nucleus of cells surrounded by a capsule of fibres. On macroscopic examination of the acoustic colliculi of the porpoise it seemed possible that the cells might have differentiated into the pattern characteristic of supra-segmental structures in the nervous system. This was not found to be the case and the reason seems quite clear. The optic colliculi differentiated in a laminated pattern in an attempt to form a

correlation centre at the time when few sensory fibres other than olfactory entered the pallium. With the development of the neocortex cell all types of sensory impulses are drawn into this region. In other words, there is a strong tendency to the development of dominant centres in the most cephalic portion of the neural tube and in the most cephalic portion of the organism.

The cochlear fibres, therefore, are the conspicuous group of sensory fibres reaching the cerebral cortex. On the basis of these acoustic impulses the temporal lobe has greatly increased in size and has grown posteriorly, carrying the lateral ventricle with it to form the inferior horn of the ventricle. Moreover, large portions of the cortex have been buried to form an island of Reil. Around the acoustic projection centre a wide correlation area has probably developed to synthetize the cochlear stimuli with other types of sensory impulses reaching the cortex.

Many sections of the cerebral cortex were cut and stained with thionin to permit of study of the cyto-architecture. It was hoped that the cortex of the porpoise could be divided into areas, each having peculiarities in the size, shape and arrangement of the cells so that regions could be recognized as clear-cut projection or correlation centres. This is possible in the cortex of Primates, including man. The cells are relatively sparse everywhere in the cortex of the porpoise and they are separated from each other by wide intervals. Moreover the layers of cells are poorly differentiated in most regions. There were a few areas having characteristic structure and these were separated by regions in which the arrangement of the cells was very primitive. In all portions of the cortex the outer, cell-free layer is wide. A definite layer of granular cells may be demonstrated in all parts except in the motor area. The infra-granular pyramidal cells show no remarkable development and the supra-granular pyramidal layer is everywhere thin. Certain areas, however, may be identified. The motor cortex lies at the very frontal pole of the cortex ; the visual projection area surrounds the calcarine fissure on the mesial tip of the occipital lobe. The acoustic fibres enter the temporal lobe just posterior to the Sylvian fissure. The region that gives rise to the temporo-pontine tract has also been identified. The fibres of cutaneous and deep sensation enter the cortex just posterior to the motor area. A great deal of the remaining cortex has a very primitive cytological pattern and this must be considered as rather undifferentiated correlation cortex.

With the rapid development of the cerebral cortex concurrent with

the acquisition of binocular stereoscopic vision in Primates, the motor cortex underwent great differentiation, particularly in reference to the innervation of the fore-leg. The fore-leg lost its locomotor and postural functions and became useful for climbing trees or carrying food to the mouth. No motor development along these lines was required in the porpoise where the hind-leg is not developed on the surface of the body and the fore-leg has differentiated into a short flapper.

Microscopic study of the cerebral cortex of the porpoise demonstrated a motor area near the frontal pole of the brain. Anterior to this one was the modified motor area, or area frontalis, which gives rise to the fronto-pontine tract. Both these areas are rather large and the area frontalis extends on to the ventral surface of the frontal lobe so that there is no frontal correlation area in the porpoise similar to that present in Primates. The cortico-spinal and fronto-pontine tracts may be followed into the cerebral peduncle as well-defined bundles. The largest efferent bundle in the cerebral peduncles is the temporo-pontine tract, which contains large numbers of fibres.

The cerebellum is of great size in the porpoise and the hemispheres, in particular, are very well developed. It is known that the cerebellar hemispheres differentiate coincidently with the cerebral hemispheres. Both are large in the porpoise and it would be expected that there would be marked connecting tracts between them. This is indeed the case as evidenced by the large sized pons. The efferent fibres from the cerebrum do not run through the pons but dorsal to it, and the fibres turn ventrally to end around the pontine cells. On the efferent side of the cerebellar reflex arc, many fibres of the brachium conjunctivum end in the thalamus and undoubtedly are relayed back to the cortex.

In connection with the cerebellum of the porpoise it is interesting to recall the theory of certain comparative anatomists that the vermis controls the trunk musculature, the hemispheres the limb musculature of the body. The porpoise has no hind-legs and the fore-legs have developed into flappers. Yet the hemispheres of cerebellum are very large.

Finally, a word concerning the efferent paths from the brain influencing the anterior horn cells of the cord. These require further study. The cortico-spinal fibres cannot be traced in sections stained by the Weigert-Pal method below the lower end of the medulla. Either they are relayed at this level or travel caudad as non-medullated fibres. The red nucleus is rather small in the porpoise, as is also the rubro-spinal tract. The vestibulo-spinal and tecto-spinal tracts are also small.

In summary, the cochlear division of the acoustic nerve shows great development in the porpoise and the acoustic nuclei and tracts in the brain-stem are very large. Large numbers of fibres carry acoustic impulses to the cortex and it is probable that these impulses have played a great part in the differentiation of the cortex of the porpoise.

Coincident with the growth of the cerebral cortex the cerebellum has become large; the hemispheres and flocculi show particular development. The connections between the cerebral and cerebellar hemispheres are well differentiated and large cortico-efferent pathways connect with the pontine cells. The porpoise is a powerful and graceful swimmer, and these pathways probably carry impulses that produce a precise control of the tone and contraction of the striated muscles of the body.

BIBLIOGRAPHY.

ADDISON, W. H. F. (1915). "On the Rhinencephalon of Delphinus delphis," *Journ. Comp. Neurol.*, **25**, 497.

CUNNINGHAM, D. J. (1877). "The Spinal Nervous System of the Porpoise and Dolphin," *Journ. Anat. and Physiol.*, **11**, 209.

DART, R. A. (1923). "The Brain of the Zeuglodontidæ (*Cetacea*)," *Proc. Zool Soc., London*, 615.

FISH, P. A. (1896). "The Brain of the Fur Seal (*Callorhinus ursinus*). Report of the Fur Seal Investigation," pt. 3, 21.

Idem. (1898). "The Brain of the Fur Seal (*Callorhinus ursinus*), with a Comparative Description of those of *Zalophys californianus*, *Phoca vitulina*, *Ursus americanus* and *Monachus tropicalis*," *Journ. Comp. Neurol.*, **8**, 57.

Idem. (1903). "The Cerebral Fissures of the Atlantic Walrus," *Proc. U.S. Nat. Museum*, **26**, 675.

HATSCHEK, R. and SCHLESINGER, H. (1902). "Der Hirnstamm des Delphins," *Arb. aus dem Neur. Instit. an der Wiener Univers.*, **9**, 1

HATSCHEK, R. (1896). "Ueber das Ruckenmark des Delphins," *Arb. aus dem Instit. für Anat. und Physiol. an der Wiener Univers.*, **4**, 286.

Idem. (1896). "Ueber den Ruckenmark des Seehundes (*Phoca vitulina*) im Vergleiche mit dem des Hundes," *ibid.*, **4**, 313

Idem. (1903). "Sehnervenatrophie bei einem Delphin," *ibid.*, **10**, 223.

HOWELL, A. B. (1930). "Aquatic Mammals," Charles G. Thomas, Springfield, Illinois.

KELLOGG, R. (1928). "The History of Whales, their Adaptation to Life in the Water," *Quart. Rev. of Biol.*, **3**, 29 and 174.

LANGWORTHY, O. R. (1931). "A Description of the Central Nervous System of the Porpoise (*Tursiops truncatus*)," *Journ. Comp. Neurol.* (in press).

MILLER, GERRIT (1923). "The Telescoping of the Cetacean Skull," Smithsonian Miscellaneous Collection, **76**, 1.

WISLOCKI, G. B. (1929). "The Hypophysis of the Porpoise (*Tursiops truncatus*)," *Arch. of Surg*, **18**, 1403.

Idem. (1929). "On the Structure of the Lungs of the Porpoise (*Tursiops truncatus*)," *Amer. Journ. Anat.*, **44**, 47.

Notices of Recent Publications.

The Selected Writings of John Hughlings Jackson. Vol. I. "On Epilepsy and Epileptiform Convulsions." Edited by James Taylor, with the assistance of Gordon Holmes and F. M. R. Walshe. London: Hodder and Stoughton. 1931. Pp. 500. Price 25s.

The increasing influence upon modern neurological thought of the ideas of Hughlings Jackson is a welcome sign that can have escaped no student of the neurological literature of this country. Of equally favourable augury for the future of neurology is the evidence that continental neurologists also are coming to appreciate the significance of Jackson's work. Thus, some years ago Arnold Pick dedicated his great contribution to the study of speech disturbances to Jackson as "the deepest thinker in neuropathology of the past century," while more recently translations of certain of his lectures have appeared in German.

All this is the more remarkable tribute to the genius of Jackson when we consider that to the present generation much of his work is a closed book. Not until 1925 was there even an available bibliography of his writings, which were to be found only by arduous search on the shelves of great medical libraries and in the columns of hospital reports and medical periodicals, many of them long since extinct. In 1925, Dr. James Taylor, the editor of the present selection of Jackson's writings, collected and re-published his shorter notes, known as "Neurological Fragments," and appended thereto a complete bibliography of his published works. In preparing the two volumes, of which the present is the first, Dr. Taylor has completed his pious task, and in doing so has earned the warm gratitude of all neurologists.

In virtue of their being so inaccessible, and because also of the abstract quality of much of Jackson's thought, his views have not infrequently been incompletely understood and ineptly cited. In this selection of his writings their author speaks for himself, and it would be unfitting, as indeed it would be impossible, to attempt within the compass of this brief notice any summary of Jackson's contribution to medicine. It may not be inexpedient, however, to consider briefly some of the lessons we may derive from his work. They are lessons of scrupulously careful clinical observation, of what Trotter has aptly described as an "unresting contemplation" of the facts of observation, and of an unparalleled degree of scientific insight.

The seas Jackson so skilfully and so triumphantly sailed were uncharted to an extent it is difficult for us of this generation to realize, yet unless we do realize this we may fail to see the magnitude of his achievement. If we are to understand the depth and the philosophic quality of his thought we must

try to recall the state of knowledge concerning the physiology of the nervous system some sixty years ago. That Jackson's views, so largely speculative when he formulated them, should have received so striking a measure of confirmation, not alone from the labours of succeeding generations of clinical observers, but also at the hands of such a master of the experimental method as Sherrington, shows upon how sound a foundation of clinical observation and clear thinking they were built. Thus, not the least of the lessons we may learn, and it is one by which each of us may profit, is the primary duty of precise and adequate clinical observation. In the logical sequence and development of his thought throughout the series of papers on convulsions, we see a rational and masterly progress from observation to generalization.

To the mind of the neurologist there will occur a small and select number of the writings of bygone masters in this branch of medicine, to which he unfailingly returns from time to time, either for the treasures of clinical wisdom and knowledge they contain, or for a stimulus and inspiration in his own work. It is in the latter class that Jackson's writings will come to occupy a unique position.

Much praise is due to Dr. Taylor for his enlightening introduction to this volume, and for the care he has taken in collecting and editing the papers it contains, and in verifying the numerous cross-references which it has been necessary to insert. Neurologists will look forward to the appearance in the coming autumn of the second volume which will contain all Jackson's publications on other neurological subjects which it is thought profitable to reprint.

The Diagnosis and Treatment of Brain Tumours. By ERNEST SACHS. London: Henry Kimpton. 1931. Pp. 396 with 224 illustrations. Price 42s.

The increasing interest in tumours of the brain, and particularly the development of neurological surgery, has led to the appearance of numerous textbooks and monographs on this subject during the past few years, and the volume under review will take an important place among them. The author is a well-known neurological surgeon who rightly insists on the necessity of a thorough training in neurology for anyone who aspires to undertake the operative treatment of intracranial growths, and his book is consequently written largely from the clinical point of view. Yet this is its most disappointing feature: the groups of symptoms which characterize lesions of different parts of the brain are recorded, often in tabular form, and some of them are discussed, but their significance and their value in localization could have been dealt with more simply and in a manner more useful to the surgeon who seeks assistance from the author's experience. The disturbances of speech, for instance, are presented mainly as extracts, occupying a few pages, from Head's monograph on aphasia, which, admirable though it is, will be of little use to the student confronted with the problem of determining the site of a lesion producing any type of aphasia. The chapter on convulsions is particularly incomplete, many of the distinguishing features of those due to local

disturbances in different regions of the brain being neglected or mentioned without due emphasis on their importance in the problem of localization. The discussion of tumours of the cerebellum also lacks that intimate relation to the symptoms seen at the bedside which can enlighten the student or surgeon as to the exact significance of his clinical observations, and unfortunately the citation of cases, typical though they may be, cannot replace this. Several obvious mistakes have crept into the clinical sections, as the explanation of a typical grasp reflex by paralysis of the extensors of the fingers.

These defects only illustrate the great difficulty in the adequate treatment of the task which the author has undertaken, for the localization of cerebral tumours by clinical methods requires all the knowledge and experience that has been acquired by neurologists within the past fifty years, and to present these properly, even in summary, and with a critical regard to their significance, is evidently impossible in a book devoted mainly to surgery. Ventriculography and other methods employed in localization are carefully described and their value indicated. The chapter on surgical pathology is excellent, though it contains little that is new. That on operative technique and post-operative treatment also represents admirably the author's methods.

Les Tumeurs cérébrales; leurs Manifestations et leur Traitement chirurgical. Par Th. de MARTEL et J. GUILLAUME. Paris: G. Doin et Cie. 1931. P. 136. Price 70 francs.

All the cases of intracranial tumour treated by operation in the Neuro-Surgical Institute of Paris, 35 in number, between December, 1929, and April, 1930, are described by the authors in this volume with few comments or remarks on the problems presented by the individual patients. Their acknowledged aim has been to present to their colleagues who have little experience of neurology the possibilities of cerebral surgery. The descriptions of the clinical symptoms and of the operative technique are meagre, but the volume contains some interesting observations. Their enthusiasm will probably be tempered by further experience; one of their main conclusions is that when an intracranial tumour is suspected further investigations may be prejudicial to the patient, even exact localization being unimportant as the line of approach is identical in all cases.

La Sciatique. Par J. A. CHAVANY. Paris: G. Doin et Cie. 1931. P. 51. Price 18 francs.

Though this small volume is devoted chiefly to its treatment, a very thorough description of the clinical features of sciatica is given and its differential diagnosis fully discussed. The clinical side of the subject is dealt with under the headings, simple or primary sciatica, which, as Sicard, he regards as due to a massive affection of a rheumatic nature of the structures through which the nerve passes in the sacrum, pelvis and hip; symptomatic sciatica, in which the pain is only a manifestation of some other disease, and pseudo-sciatica.

The section on treatment contains a comprehensive review of the therapeutic measures that have been used with success, much attention is being given to local and paravertebral injections.

Les Syndromes cérébelleux mixtes. Par A. de ALMEIDA PRADO. Paris : Masson et Cie. 1931. P. 168. Price 30 francs.

This volume by a recently deceased Brazilian neurologist has been admirably translated into French by Dr. Nathan. It is based entirely on French work, and includes those clinical conditions not due to the primary disease of the cerebellum, in which, however, symptoms of disturbance of cerebellar functions are a prominent feature. The so-called syndromes of the superior, middle and inferior peduncles of the cerebellum, those due to the compression of the cerebellum, and those which appear occasionally in other diseases, as general paralysis, encephalitis lethargica and disseminated sclerosis, are described in separate chapters. The author's personal experience has evidently been small, in fact his book consists almost entirely of extracts of French literature made with little evidence of critical discrimination. The subject is presented as a series of "syndromes," many of which are based on a single clinical observation and recorded without regard to their physiological significance and often, too, of their anatomical substratum. The uncritical inclusion of all published cases relevant to his subject and the neglect of most of the recent work which has not appeared in French literature naturally robs the book of much of the value it might have had, but it contains a number of extracts of observations that may be useful to neurologists interested in the symptomatology of lesions of the brain-stem.

Die beginnende Paralyse : eine klinische und psychopathologische Studie. Von H. BÜRGER PRINZ. Berlin: J. Springer. 1931. S. 86. Price RM. 7.80.

The important question whether the clinical form of early dementia paralytica has any prognostic importance for treatment by malaria is one of the main subjects of this monograph, but it contains an interesting analysis of the various types of the early disease, before and after treatment, and especially of their psychological aspects. From his investigation of fifty-six cases, the author believes that the prognosis is bad in depressive and hypomaniacal cases, and in those with evidences of general dementia and pronounced symptoms of organic disturbance. A chapter on the nature of the dementia and the factors that influence or contribute to it is an excellent essay to a matter of great interest.

The Inborn Factors in Disease: an Essay. By ARCHIBALD E. GARROD. Oxford University Press. 1931. Pp. 160. Price 7s. 6d.

This little book on predisposition to disease makes no attempt at being an exhaustive treatise on the subject. After a historical survey of the various

interpretations or uses of the word "diathesis" it is divided into two parts, the first on the basic principles of predisposition and the second on the several kinds of predisposition. A very suggestive chapter is that on the chemical basis of individuality; and in that on "the inborn factors in infective diseases" the physician whose conception of a disease is dominated by its ætiology will find much food for thought. The author's bias towards biochemistry is everywhere apparent, but errors of metabolism form a small part only of the subject matter. It is disappointing that the word "abiotrophy" is still used without any attempt at explaining it in terms of metabolism; the author merely suggests the possibility that the tissues "may be damaged or rendered sensitive to damage, by the presence in them of some metabolic product which progressively impairs their integrity." Obviously it is too early yet for us to envisage life altogether in terms of chemistry, but the author sees in biochemistry the best approach to the study of mutations and hereditary predispositions.

The Science of Psychology. Introductory Study. By RAYMOND H. WHEELER. London: Jarrolds, Ltd. 1931. Pp. 556. Price 21s.

Professor Raymond Wheeler has written a textbook which should prove of great value to students who have already acquired a basic knowledge of modern psychology. The excellence of the book lies not so much in the broad field which has been covered with a considerable degree of detail, as in the fairness with which the various schools of thought are discussed, and the clarity of the exposition. The exposition is in a way unique in that it starts off with a lengthy chapter on social behaviour before passing on to deal with the manifestations of individual psychology. Emotive behaviour and intellectual behaviour are fully dealt with under various heads, and wherever the subject needs further elucidation the student is liberally supplied with references. The important subject of learning is discussed, with its experimental methods, in two long chapters. The latter part of the book deals with what he calls observational behaviour, that is to say, with the characteristics of sensory experience and perception. The book ends with an up-to-date treatment of the nervous system and its relation to behaviour.

This order of exposition is particularly attractive in that it leaves the Behaviouristic approach to human behaviour to the end after the student has acquired a knowledge of psychological processes as seen by observation and introspection. In other words, the theory of Behaviourism, as expressed in neurology, is brought out without giving the reader an initial bias. Each chapter has an excellent bibliography.

Die Denkmethoden und ihre Gefahren. By VERA STRASSER. Leipzig: Georg Thieme. Pp. 526. Price 20 marks.

This large volume deals with the complexity of human psychological reactions in their various departments of human life. The burden of the book is to bring into relief the methods of investigating psychological disturbances

and the dangers inherent in such methods. In carrying out this stupendous task, the author has plumbed the depths of philosophical analysis, not only of the methods, but of the concepts used in psychological discussion. The book can be recommended only to those psychopathologists who have philosophic training and plenty of time.

Conditions and Consequences of Human Variability. By RAYMOND DODGE. New Haven: Yale University Press. Pp. 162. Price $2.50

Although Professor Dodge attacks the problem of human behaviour and its variability in a distinctly philosophic manner, he is in constant contact throughout this book with the modern problems of functional neurology. He is conscious, as many are, of the methodological difficulties underlying both neurology and psychology, and his restatement in this monograph of our present-day knowledge of the integrative action of the nervous system, and its relation to psychology, is very welcome. He deals at the outset with the general problem of variability with reference to sensibility and the conditioning of responses. He then passes on to a consideration of relative fatigue, and the refractory phase. Inhibition and summation are subtly discussed in the light of the latest work of Lucas, Adrian, Forbes, and Pavlov. The effect of faint stimuli has a chapter to itself, and its psychological implications are touched upon. In dealing with cortical function, in particular, his consideration of the interaction of neural strata and of cortical systematization is particularly suggestive to all those who wish for a closer liaison between neurology and psychology. The book closes with a philosophical discussion of the relationship of mind and brain. This is a book that can be highly recommended to all those who regard neurology as something more than the study of organized grey matter. It can be called the study of dynamic neurology.

Handbuch der Geisteskrankheiten. Herausgegeben VON OSWALD BUMKE. 5ter Band. Spez. Teil 1. Seiten 578 mit 10 Abbildungen. Berlin: J. Springer. 1928.

Handbuch der Geisteskrankheiten. Herausgegeben VON OSWALD BUMKE. 10ter Band. Spez. Tiel 6. Seiten 374 mit 64 Abbildungen. Berlin: J. Springer. 1928. Price RM. 36.00.

Like the other parts of this System of Psychiatry, the present volumes are critical and thorough, inclining to conservatism wherever speculation seems to have outrun the data of immediate observation. In Volume V the psychopathic reactions and dispositions are presented in great detail, with an introductory account by Birnbaum of the modern views on the structure of psychosis. A short section by Stertz on the neurasthenic reaction is followed by J. H. Schultz's attempt, on the whole a successful one, to describe the ill-defined condition "constitutional nervousness": for him it is a diagnosis made by

elimination, though with genetic and constitutional implications. The succeeding two sections cover the whole range of neurosis and psychopathic disposition: the customary divisions into hysteria, compulsion neurosis, anxiety forms, etc., are sacrificed for a less formal mode of presentation, with the emphasis on proneness to react along comprehensible lines according to constitution and previous experience. None of the rigid formulations, however assertive, complex or "dynamic," are accepted as adequate and final in the general section by E. Braun on "Psychogenic Reactions," while Eugen Kahn's exhaustive monograph on "Psychopathic Personalities" is of remarkable breadth and restraint.

The concluding section on Psychotherapy has been written by J. H. Schultz, who shows that successful treatment of these disorders is not by any means the prerogative of well-meaning enthusiasts or jargon-equipped muddlers, and that treatment may be not only successful but even intelligent without being limited by the tenets of one school.

The first half of Volume X deals with congenital mental defect, and defect acquired in early childhood. The section on the psychotic complications is rather short for so comprehensive a study; and in the unduly concise description of intelligence tests there is, as elsewhere, scant regard for non-German work. The author's criticism of the mental-age method of assessing defect is, however, trenchant and deserves emphasis. Mental disorders associated with thyroid deficiency are described at rather disproportionate length by Gamper and Scharfetter: congenital and infantile myxœdema and endemic cretinism are of only limited interest outside the areas where they are common. The work has been carefully done and will be of interest to the specialist in thyroid disorders.

Psychotherapie bei organischen Erkrankungen. By FRITZ MOHR. Leipzig: Georg Thieme. 1930. Pp. 103. Price 3 marks.

This is a slender and attractive volume on a topic which has only too belatedly come to the front. It deals with the treatment of the psychological accompaniments of physical diseases, and in addition, although in a less degree, with the occasional psychological causes which may precipitate organic disease. It opens with a discussion of general psychopathological considerations and then passes on to the physical and mental methods of dealing with organic diseases. Hypnosis, psycho-analysis, waking suggestion, and re-education are fully discussed. The final chapter deals with particular disorders and actual examples of cases.

Brain and Personality. By PAUL SCHILDER, M.D., Ph.D. Nervous and Mental Disease Publishing Company: New York and Washington. 1931. Pp. 136. Price $3.00.

The first part of this book deals with the psychological aspect of cerebral neuropathology; it is a summary of the author's views on the relationship

between psychic and organic, as presented in numerous earlier publications, and contains chapters on speech disturbance, optic agnosia, tone and posture, and consciousness. They are in the main loosely connected studies, with evidence of wide reading and bold, if stimulating, thought.

The other part, on the relation between the personality and the motility of schizophrenics, is built around clinical observations, reported in some detail. The chief objection to Schilder's method is that he correlates phenomena which may be of different nature, and from this correlation infers a similarity in the functional change and morphological substrate. His chief effort is to bring about a synthesis, or to find a common explanation for "the problems of the motility and the problems of the emotions of the schizophrenic," but there is a more or less tacit assumption that the latter are the prime movers.

L'Hallucination. Par PIERRE QUERCY. Philosophes et Mystiques, pp. 381. Etudes cliniques, pp. 560. Paris: Felix Alcan. 1930.

This large work is a semi-philosophical treatise dealing not merely with hallucinations in the strict sense but with the whole problem of sensation and perception. The first volume is concerned mainly with the systems of three philosophers, Spinoza, Leibnitz and Bergson, and the experience of one mystic, the famous Saint Theresa de Ahumada. After discussing the arid speculations of the philosophers, Quercy turns to the autobiography of that remarkable woman, lately the subject of renewed interest in France. He examines her visions and those of St. John of the Cross, from the point of view of the theologian as well as of the philosopher and the clinician, and adduces the relevant doctrine of the mediæval schoolman, Gerson.

The second volume, of clinical studies, covers a wide field: coloured vision, hypnagogic hallucinations, dreams, the phenomena of mescalin and other intoxications, and illusions of many kinds are among the objects of the author's restricted method of investigation. The work of E. R. Jaensch, on eidetic imagery, has a valuable, rather sceptical chapter to itself.

These subtle and skilfully written volumes represent a method of approach which is not that of the psychiatrist or the neurologist, but is none the less sound and, from the point of view of epistemology, essential.

Das Stehen. Statische Reaktionen, Gleichgewichtsreaktionen und Muskeltonus unter besonderer Berücksichtigung ihres Verhaltens bei kleinhirnlosen Tieren. Von. G. G. J. RADEMAKER. S. 476 mit 296 Textfiguren. Berlin: J. Springer. 1931. Price Rm. 69.60.

Recently the editors of the *Journal of Pathology* have sought to impress upon their contributors the duty of brevity, by printing in a number of the Journal the following anonymous aphorism:—

> "Buddha wrote nothing. Christ but once, in the dust.
> The 'Agricola' of Tacitus contains only 7,000 words,
> and the whole of Thucydides would go into a large
> issue of the *Times*."

Even the most determined reader, faced by this mighty monograph of some 200,000 words, must wonder whether what its writer has to contribute to knowledge might not have been more concisely conveyed.

In the student of so complex and highly technical a subject as that dealt with by Professor Rademaker, it is surely reasonable to assume a working acquaintance with the relevant literature and a thorough knowledge of those pioneer investigations of Sherrington and Magnus out of which it has arisen. Yet in page after oppressive page of small, close-knit type we are given all that has been written, profitably and otherwise, by experimentalists and clinicians upon every aspect of the subject. With a literature that grows almost faster than any interested student can master it, ultimately it will ensue that if every writer is to cumber his own fresh additions to knowledge with an up-to-date history of his subject, papers and monographs will soon reach dimensions that will defy the printer and eliminate all readers.

Further, in his original papers and in the monograph that so admirably crowned his investigations, Professor Magnus conceded to his readers the inestimable boon of a concise summary of its principal contents at the end of each chapter. Not the least of the obstacles that Professor Rademaker places between his readers and himself is the withdrawal of this aid to easy and comfortable study.

Nevertheless, those who are sufficiently keen to follow the author will find an important contribution to the physiology of posture, and a careful analysis of the symptomatology of cerebellar extirpation in animals.

In briefest summary, Rademaker finds that after extirpation of the cerebellum, all those postural and stato-kinetic reactions that underlie the maintenance and harmonious variation of posture in the intact animal persist. There is no loss of these reactions, but a "release" of activity in which the reactions take on features of excess and of impaired maintenance and adjustment. He rejects as elementary components of the syndrome of cerebellar defect, the astasia, atonia and asthenia of Luciani, regarding these phenomena when they are seen at all as transient, and of the order of "shock" symptoms.

But while such a minute analysis of cerebellar ataxy as he has achieved is an essential preliminary to any conclusive and detailed theory of cerebellar function, it does not appear that such a theory is yet within reach. Rademaker contents himself with the general statement that the cerebellum exerts a regulating influence not only upon those co-ordinated muscular reactions that are subserved by the brain-stem and cord and arise in exteroceptive and proprioceptive stimuli, but also upon reactions arising in the distance receptors and traversing the cerebral cortex. He rejects the hypothesis that the cerebellum is no more than an instrument by which the cerebral cortex analyses and synthesizes the reflex reactions mediated through the brain-stem and cord, in the production of normal voluntary movement.

The observation of Magnus and others that the well co-ordinated and highly complex motor reactions of the thalamus animal are not disordered by subsequent decerebellation have made it seem probable that the cerebellum

does not function in the absence of the fore-brain and thus does not participate in the fundamental processes of co-ordination of movement. Rademaker has made but a single experiment to test this hypothesis, and on the basis of this observation he rejects it. The experiment consisted in extirpating the cerebellum in a dog from which the fore-brain had already been removed some weeks earlier. This dog after the cerebral extirpation presented the well-known activities of a dog without a fore-brain, but after the subsequent decerebellation its movements presented all the essential features of cerebellar deprivation in an otherwise intact animal. The animal succumbed to infection some five weeks after the last-named operation. We are not justified, therefore, in accepting as final the result of an isolated and prematurely terminated observation. But if it be confirmed by further and more conclusive experiments, its bearing upon our conception of cerebellar function will be of the first importance.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.